CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	207,078
Drug Name:	LOKELMA (sodium zirconium cyclosilicate) 5g and 10g powder packet
Indication(s):	Treatment of hyperkalemia
Applicant:	ZS Pharma, Inc.
Date(s):	Submission date: 05/26/2015 PDUFA due date: 05/26/2016
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
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Keywords: clinical studies, multi-center

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1 EXECUTIVE SUMMARY

The three efficacy studies reviewed (ZS-002, ZS-003, ZS-004) provide strong statistical support for the capacity of sodium zirconium cyclosilicate (ZS) to lower potassium levels in an acute setting (within 48 hours) and maintain such lowered levels at a reduced dosing frequency for an extended duration (several weeks). A dose response relationship has been observed for the efficacious doses of 5, 10 and 15 g of ZS.

The sponsor pre-specified a multiple comparison control procedure for the primary efficacy endpoint for each of the three studies reviewed, but failed to do so for the secondary efficacy endpoints in Study ZS-003. Secondary efficacy endpoint results for Study ZS-003 can only be regarded as exploratory because the type I error is not controlled overall.

2 INTRODUCTION

2.1 Overview

Hyperkalemia is an electrolyte disorder resulting from excessive production (oral intake, tissue breakdown) or insufficient elimination of potassium (S-K). Hyperkalemia is associated with serious, potentially lethal cardiac arrhythmias, conduction system abnormalities, and increased mortality. According to the sponsor sodium zirconium cyclosilicate (ZS) powder for oral suspension is a highly selective cation exchanger that entraps potassium in the gastrointestinal tract in exchange for sodium and hydrogen.

The clinical development program for ZS includes three completed multicenter studies that evaluated the efficacy and safety of ZS (Study ZS-002, ZS-003, and ZS-004). ZS-002, a phase 2 study, was conducted in the United States, whereas the phase 3 studies ZS-003 and ZS-004 were conducted in the United States, Australia, and South Africa.

Each of the completed studies included an Acute Phase (48 hours up to 96 hours in Study ZS-002 and 48 hours in Studies ZS-003 and ZS-004) in order to normalize S-K values. In the phase 3 studies, subjects who completed the Acute Phase with normalized S-K were eligible for extended dosing and were randomized to treatment for an additional 12 days in Study ZS-003 (Subacute Phase) and an additional 28 days in Study ZS-004 (Maintenance Phase), in both cases employing a randomized, withdrawal design. In Studies ZS-002 and ZS-003, the Acute Phase was conducted in a randomized, placebo-controlled, double-blind fashion. The Acute Phase of Study ZS-004 was open-label, with a single group of ZS 10g.

Table 1. List of all Studies Included in Analysis

Study Number	Phase and Design	Treatment Period	# of Subjects per Arm	Study Population
ZS-002	Phase 2, parallel	At least 48 hours, at most 96 hours	ZS 0.3g: 12 ZS 3g: 24 ZS 10g: 24 Placebo: 30	Hyperkalemic adults
ZS-003	Phase 3, parallel	Acute Phase: 48 hours; Subacute Phase: 12 days	Acute Phase: ZS 1.25g: 154 ZS 2.5g: 141 ZS 5g: 157 ZS 10g: 143 Placebo: 158	Hyperkalemic adults
ZS-004	Phase 3, parallel	Acute Phase: 48 hours; Maintenance Phase: 28 days	Maintenance Phase: ZS 5g: 45 ZS 10g: 51 ZS 15g: 56 Placebo: 85	Hyperkalemic adults

(Source: Reviewer's summary based on sponsor's study reports)

ZS-002

Study ZS-002 is a multicenter, prospective, randomized, placebo-controlled, double-blind dose escalating Phase 2 clinical trial to investigate the safety, tolerability and pharmacodynamics of ZS in subjects with mild hyperkalemia in chronic kidney disease and moderate kidney dysfunction. The study was conducted at 9 centers in the United States from November 2011 through May 2012. A total of 90 subjects were randomized (30 placebo, 12 ZS 0.3 g three times a day [TID], 24 ZS 3 g TID, 24 ZS 10 g TID).

ZS-003

Study ZS-003 is a Phase 3 multicenter, prospective, randomized, placebo-controlled, double-blind, dose ranging trial to investigate the safety and efficacy of ZS in subjects with mild to moderate hyperkalemia. The study was conducted between November 2012 and October 2013 at 65 sites in the United States, Australia and South Africa.

ZS-004

Study ZS-004 is a Phase 3 multicenter, multi-phase, multi-dose, prospective, randomized, double-blind, placebo-controlled maintenance trial to investigate the safety and efficacy of ZS in

subjects with hyperkalemia. This study was ongoing from March to August 2014 at 44 sites in the United States, Australia and South Africa.

2.2 Data Sources

Link to submission: \\CDSESUB1\evsprod\NDA207078\0000

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The Statistical Analysis Plans for the three studies under review were finalized before the last subject completed the respective study (i.e., before database lock and unblinding). The applicant submitted documentation regarding data quality control/assurance procedures in the study reports. The inspection of selected study sites (i.e., 001, 081, and 4032) by the Division of Scientific Investigation did not reveal any critical issues. The randomization process for each respective study appears correct (see appendix for basic evaluations). Spot checks for Studies ZS-003 and ZS-004 did not reveal any discrepancy between the SDTM datasets and the ADAM datasets used for the primary analyses.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

ZS-002

The primary objectives of Study ZS-002 were to evaluate the safety, tolerability, and efficacy of 3 different doses of ZS administered three times daily (TID) for 48 hours to subjects with moderate chronic kidney disease and mild hyperkalemia (S-K between 5 to 6.0 mmol/L). One of the secondary objectives was to identify the optimal dose to take into subsequent studies.

Ninety (90) subjects were enrolled in the study where they were randomized to receive escalating doses of ZS (0.3 g, 3 g, and 10 g) or placebo, administered TID daily with meals (three separate cohorts; Table 2). Safety and tolerability were assessed by an independent Data Safety

Monitoring Board (DSMB) after completion of each cohort, and before escalation to the next dose level was to be allowed.

Table 2. Dose Group Summary [ZS-002]

Cohort	Total No. Subjects/Group	No. Subjects Receiving ZS (dose)	No. Subjects Receiving Placebo (dose)
1	18	12 (0.3 g)	6 (3.0 g)
2	36	24 (3.0 g)	12 (3.0 g)
3	36	24 (10.0 g)	12 (3.0 g)

(Source: ZS-002 Study Report p. 22)

The primary efficacy endpoint was the difference in the exponential rate of change in S-K levels during the initial 48 hours of study drug treatment between the placebo-treated subjects and the ZS-treated subjects.

ZS-003

(b) (4)

according to the sponsor the lower dosages of 1.25g and 2.5g have been included to better define the dose response relationship as well as define the minimum effective dose [ZS-003 SAP p. 18].

The study consisted of a 48 hour acute phase and a 12 day subacute phase for the subjects who achieved normokalemia at the end of the acute phase. Subjects were randomized to placebo, ZS 1.25 g, 2.5 g, 5 g, or 10 g in the acute phase and would randomly either continue with this treatment in the subacute phase or switch to placebo. Dosing during the acute phase was three times a day, whereas only one dose of drug was administered during the subacute phase. Acute phase placebo subjects were switched to either 1.25 g or 2.5 g of ZS in the subacute phase.

For the acute phase, the primary efficacy endpoint is the difference in the exponential rate of change in S-K levels during the initial 48 hours of study drug treatment between the placebo treated subjects and the ZS treated subjects.

For the subacute phase, the primary efficacy endpoint is the difference in the exponential rate of change in S-K levels over the 12 day treatment interval between those on subacute therapy and

randomized withdrawal, separately for the four acute phase active treatments (excluding acute phase placebo).

ZS-004

Subjects with hyperkalemia were enrolled in the open-label acute phase and were treated with ZS 10 g TID for the initial 48 hours (6 doses). Subjects who achieved normokalemia during the acute phase were randomized in a double-blind manner in a 4:4:4:7 ratio to 1 of 3 doses of ZS (5 g, 10 g, or 15 g) or placebo administered once a day [QD] for a further 28 days. Subjects were to return to the site on maintenance phase Study Days 2, 5, 8, 12, 15, 19, 22, 26, and 29 in a fasting state for potassium measurements.

The primary efficacy endpoint was the model-based least squares mean (LSMEAN) of all available S-K values during maintenance phase Study Days 8 to 29. The secondary efficacy endpoints for the maintenance phase included the number of normokalemic days during maintenance phase Study Days 8 to 29 and the proportion of subjects who remained normokalemic at maintenance phase Study Day 29.

3.2.2 Statistical Methodologies

ZS-002

All analyses were performed according to an intent-to-treat (ITT) principle to account for all randomized subjects. A closed testing procedure was used to test from highest to lowest dose for the primary efficacy endpoint. The primary efficacy endpoint was the rate of decline of S-K levels through 48 hours. The exponential rate of decline was estimated using a longitudinal model with time and time by treatment as predictors. All serial observations post-baseline were used relative to the baseline.

ZS-003

Separate study hypotheses apply for the acute and subacute phases. Both study phases assessed the mean rate of change (log scale) for serum potassium post randomization using a random slopes model. All potassium analyses are based on the S-K values from the central laboratory.

Acute Phase

Acute testing for the primary efficacy endpoint was performed using a longitudinal model (SAS PROC MIXED) to evaluate the exponential rate of change for comparing each active dose vs. placebo. The log of the potassium level is the dependent variable. The etiology of the hyperkalemia is included as a covariate (chronic kidney disease, congestive heart disease, diabetes mellitus, and polypharmacy). The random effects are intercept and time with an unstructured covariance matrix. The coefficients for the time by treatment interaction for each dose are tested against those for the placebo, in order from the highest dose to the lowest dose until there is a non-significant test.

Subacute Phase

The two-sided hypotheses (one test per acute dose group) tests whether continuation of treatment is beneficial after initial normalization of serum potassium. The exponential model (SAS PROC MIXED) was used to evaluate the primary efficacy endpoint. Patients initially treated with placebo were excluded from the analysis as well as patients that did not normalize. The random effects are the same but the fixed effects are initial dose, time, the interaction between initial dose and time and the three-way interaction between an indicator for active drug, initial dose and time. In this model, the difference between the slope of the active drug and the slope of placebo is estimable for each acute phase dose. Thus it can be tested whether the active drug slope and the placebo slope are different for each of the acute phase dosages. This test of the primary efficacy endpoint is performed starting with the highest acute phase dose until statistical significance is no longer achieved.

ZS-004

The primary population for efficacy analysis was the maintenance phase Intent-to-Treat (ITT) population. Separate analyses were performed for the open label acute phase and the double-blind maintenance phase. Type I error was controlled at 0.05 by the use of a closed, prospectively defined procedure. There were 13 statistical comparisons included in the following closed testing order:

1) Acute Phase S-K exponential rate of change from baseline through 48 hours, 2-4) mean S-K value during Maintenance Phase Study Days 8 to 29 (ZS 15 g QD versus placebo, ZS 10 g QD

versus placebo, ZS 5 g QD versus placebo), 5-7) total number of normokalemic days during Maintenance Phase (ZS 15 g QD versus placebo, ZS 10 g QD versus placebo, ZS 5 g QD versus placebo), 8-10) proportion of normokalemic subjects on Maintenance Phase Study Day 29/Exit (ZS 15 g QD versus placebo, ZS 10 g QD versus placebo, ZS 5 g QD versus placebo), 11-13) mean S-K standard deviation during the Maintenance Phase (ZS 15 g QD versus placebo, ZS 10 g QD versus placebo, ZS 5 g QD versus placebo).

Acute Phase (Open label)

The exponential rate of change in S-K values was derived from a mixed effect model of serial S-K values during the acute phase (log-transformed) on time, baseline eGFR, chronic kidney disease (CKD) status, heart failure (HF) status, renin-angiotensin-aldosterone system (RAAS) inhibitor use, diabetes status, and age.

Maintenance Phase

The primary efficacy endpoint (mean of the Day 8-29 S-K values) was analyzed with a longitudinal model that simultaneously compared each active dose versus placebo control. The statistical model included an unstructured variance covariance matrix with subject as a random effect and fixed effects for maintenance phase treatment group, acute phase baseline eGFR, acute phase and maintenance phase baseline S-K, age (< 55, 55 to 64, > 65 years), and binary indicators for RAAS inhibitor use, CKD, HF, and diabetes mellitus. The least squares means of the treatment effect with the observed margins were used to estimate the primary efficacy parameter.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

ZS-002

A total of 90 subjects (38 females, 52 males) with CKD and hyperkalemia were randomized to treatment in the study. All 90 subjects received all doses per protocol and all subjects had S-K measurements performed at screening (Study Day -1), at baseline (pre-dose on Study Day 1) and at the time of the primary endpoint at 48 hours; hence, all subjects were included in all analyses according to the ITT principle (Table 3). All subjects completed all 7 days of study assessments.

Table 3. Subject Disposition – All Randomized Subjects [ZS-002]

	Number (%) of Subjects				
	Combined Placebo (N = 30)	**Cohort 1 ZS 0.3 g TID (N = 12)**	**Cohort 2 ZS 3 g TID (N = 24)**	**Cohort 3 ZS 10 g TID (N = 24)**	**Combined ZS (N = 60)**
Randomized	30	12	24	24	60
Treated	30 (100.0)	12 (100.0)	24 (100.0)	24 (100.0)	60 (100.0)
Completed study	30 (100.0)	12 (100.0)	24 (100.0)	24 (100.0)	60 (100.0)
Discontinued study	0	0	0	0	0

(Source: ZS-002 Study Report p. 48)

Among all subjects, the mean age was 71.1 years (range: 42 to 96 years) and most were white (98%) [Table 4].

Table 4. Demographic and Baseline Characteristics – ITT [ZS-002]

Demographic Parameter Statistic	Combined Placebo (N = 30)	Cohort 1 ZS 0.3 g TID (N = 12)	Cohort 2 ZS 3 g TID (N = 24)	Cohort 3 ZS 10 g TID (N = 24)	Combined ZS (N = 60)	Combined Placebo and ZS (N = 90)
Age at screening (years)						
Mean (SD)	69.7 (10.96)	70.3 (6.91)	72.0 (6.31)	72.3 (11.66)	71.8 (8.83)	71.1 (9.59)
Median	71	73	72	76	73	73
Min, max	42, 96	58, 80	57, 84	52, 93	52, 93	42, 96
Gender, n (%)						
Male	23 (76.7)	6 (50.0)	14 (58.3)	9 (37.5)	29 (48.3)	52 (57.8)
Female	7 (23.3)	6 (50.0)	10 (41.7)	15 (62.5)	31 (51.7)	38 (42.2)
Race, n (%)						
White	29 (96.7)	12 (100.0)	24 (100.0)	23 (95.8)	59 (98.3)	88 (97.8)
Black or African American	1 (3.3)	0	0	0	0	1 (1.1)
American Indian or Alaska Native	0	0	0	1 (4.2)	1 (1.7)	1 (1.1)
Weight at baseline[a] (kg)						
Mean (SD)	95.15 (22.122)	84.76 (18.002)	88.96 (22.002)	86.59 (26.311)	87.17 (22.839)	89.83 (22.794)
Median	90.8	86.5	83.7	78.3	81.1	86.5
Min, max	57.1, 149.7	49.4, 110.2	59.3, 138.4	52.6, 164.9	49.4, 164.9	49.4, 164.9
GFR at Study Day 0[b] (mL/min)						
Mean (SD)	45.6 (9.05)	46.2 (4.99)	46.8 (7.14)	43.5 (9.01)	45.4 (7.64)	45.4 (8.09)
Median	47	46	46	42	44	45
Min, max	30, 62	40, 57	34, 60	31, 62	31, 62	30, 62
S-K at screening[c] (mmol/L)						
Mean (SD)	5.19 (0.301)	5.25 (0.144)	5.11 (0.328)	5.13 (0.378)	5.15 (0.323)	5.16 (0.314)
Median	5.1	5.3	5.0	5.0	5.1	5.1
Min, max	4.8, 6.0	5.0, 5.5	4.6, 5.9	4.6, 6.0	4.6, 6.0	4.6, 6.0

(Source: ZS-002 Study Report p. 50)

ZS-003

Overall, 1433 subjects were screened for entry into Study ZS-003. Of those, 754 were randomized in the acute phase of the study (158 placebo, 154 1.25 g, 141 2.5 g, 158 5 g, 143 10

g) [Table 5]. A total of 18 subjects prematurely discontinued during the acute phase (the main reasons were: withdrawal of consent, hyperkalemia, and adverse event) [Table 6].

Table 5. Acute Phase: Subject Populations - All Randomized Subjects [ZS-003]

Population	Placebo	ZS 1.25 g TID	ZS 2.5 g TID	ZS 5 g TID	ZS 10 g TID
Randomized	158	154	141	158	143
Treated, n (%)	158 (100)	154 (100)	141 (100)	157 (99.4)	143 (100)
Safety, n (%)	158 (100)	154 (100)	141 (100)	157 (99.4)	143 (100)
ITT, n (%)	158 (100)	154 (100)	141 (100)	157 (99.4)	143 (100)

(Source: ZS-003 Study Report p. 72)

Table 6. Acute Phase: Subject Disposition – All Randomized Subjects [ZS-003]

Disposition, n (%)	Placebo	ZS 1.25 g TID	ZS 2.5 g TID	ZS 5 g TID	ZS 10 g TID
Randomized	158	154	141	158	143
Treated	158 (100)	154 (100)	141 (100)	157 (99.4)	143 (100)
Completed Acute Phase	157 (99.4)	150 (97.4)	137 (97.2)	152 (96.2)	140 (97.9)
Discontinued Acute Phase	1 (0.6)	4 (2.6)	4 (2.8)	6 (3.8)	3 (2.1)
Adverse event	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	1 (0.7)
Consent withdrawn	0 (0.0)	1 (0.6)	1 (0.7)	4 (2.5)	0 (0.0)
Subject compliance	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Sponsor's decision	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Hypo- or hyperkalemia	1 (0.6)	1 (0.6)	3 (2.1)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)[a]	0 (0.0)

(Source: ZS-003 Study Report p. 68)

All subjects who completed the acute phase and had potassium values within the normal range (3.5 to 4.9 mmol/L) were eligible to enter into the subacute phase. Greater proportions of subjects in the placebo and the lowest ZS dose group did not achieve normokalemia following the acute phase compared to the higher ZS doses (placebo 38.6%, 1.25 g 39%, 2.5 g 25.5%, 5 g 11.4%, 10 g 10.5%) [Table 7].

Table 7. Acute Phase: Subjects Who Did Not Enter Subacute Phase By Reason – All Randomized Subjects [ZS-003]

Reason, n (%)	Placebo (N = 158)	ZS 1.25 g TID (N = 154)	ZS 2.5 g TID (N = 141)	ZS 5 g TID (N = 158)	ZS 10 g TID (N = 143)
Did not enter Subacute Phase	61 (38.6)	60 (39.0)	37 (26.2)	19 (12.0)	16 (11.2)
Consent Withdrawn	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.7)
Sponsor's Decision	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Hypo- or Hyperkalemia	61 (38.6)	60 (39.0)	36 (25.5)	18 (11.4)	15 (10.5)

(Source: ZS-003 Study Report p. 69)

Of those patients who were eligible for the subacute phase more than 90% in each treatment group completed it. Reasons for discontinuation included adverse events and consent withdrawal [Table 8].

Table 8. Subacute Phase: Subject Disposition – All Randomized Acute Phase ZS Subjects [ZS-003]

	Acute Phase Treatment							
	ZS 1.25 g TID		ZS 2.5 g TID		ZS 5 g TID		ZS 10 g TID	
	Subacute Phase Treatment							
Disposition, n (%)	**Placebo**	**ZS QD**	**Placebo**	**ZS QD**	**Placebo**	**ZS QD**	**Placebo**	**ZS QD**
Randomized	41	49	46	54	68	65	61	63
Treated	41 (100)	49 (100)	46 (100)	54 (100)	68 (100)	65 (100)	61 (100)	63 (100)
Completed study	38 (92.7)	48 (98.0)	43 (93.5)	52 (96.3)	66 (97.1)	59 (90.8)	58 (95.1)	61 (96.8)
Discontinued study	3 (7.3)	1 (2.0)	3 (6.5)	2 (3.7)	2 (2.9)	6 (9.2)	3 (4.9)	2 (3.2)
Adverse event	1 (2.4)	1 (2.0)	1 (2.2)	1 (1.9)	1 (1.5)	4 (6.2)	1 (1.6)	1 (1.6)
Consent withdrawn	1 (2.4)	0 (0.0)	2 (4.3)	0 (0.0)	1 (1.5)	0	1 (1.6)	1 (1.6)
Protocol violation	1 (2.4)	0 (0.0)	0	0	0 (0.0)	1 (1.5)	0	0
Investigator's decision	0	0	0	1 (1.9)[a]	0	0	0	0
Hypo or hyperkalemia	0	0	0	0	0	0	1 (1.6)	0
Death	0	0	0	0	0	1 (1.5)	0	0

(Source: ZS-003 Study Report p. 73)

Demographics

A summary of demographic and other baseline characteristics for the acute phase of Study ZS-003 is presented by treatment group in Table 9 for the ITT population. The demographic characteristics were generally similar among the acute phase treatment groups (mean age ranged from 65.2 to 66.2, majority of patients were male [53.9 to 64.5%], and most were White [83.9% to 88.7%]). Within each treatment group the greatest proportion of subjects had baseline S-K values ≤ 5.3 mmol/L (range: 49.4 to 65.7%). The most common etiologies of elevated S-K are CKD (based on eGFR < 60 mL/min: 75%), RAAS inhibitor medication (67%), and diabetes mellitus (60%).

Table 9. Acute Phase: Demographic and Other Baseline Characteristics –ITT [ZS-003]

Demographic Parameter Statistic	Placebo (N = 158)	ZS 1.25 g TID (N = 154)	ZS 2.5 g TID (N = 141)	ZS 5 g TID (N = 157)	ZS 10 g TID (N = 143)
Age at screening (years)					
Mean (SD)	65.6 (12.24)	65.4 (13.07)	65.9 (11.73)	65.2 (11.91)	66.2 (12.16)
Median	66.5	66.0	67.0	66.0	68.0
Min, max	27.0, 88.0	22.0, 93.0	27.0, 91.0	24.0, 89.0	31.0, 91.0
Gender, n (%)					
Male	98 (62.0)	83 (53.9)	91 (64.5)	96 (61.1)	80 (55.9)
Female	60 (38.0)	71 (46.1)	50 (35.5)	61 (38.9)	63 (44.1)
Race,[a] n (%)					
White	136 (86.1)	131 (85.1)	125 (88.7)	132 (84.1)	120 (83.9)
Black or African American	17 (10.8)	20 (13.0)	11 (7.8)	20 (12.7)	19 (13.3)
Asian	2 (1.3)	0	5 (3.5)	3 (1.9)	2 (1.4)
American Indian or Alaska Native	2 (1.3)	0	0	1 (0.6)	1 (0.7)
Native Hawaiian or other Pacific Islander	1 (0.6)	3 (1.9)	0	0	1 (0.7)
Other	0	0	1 (0.7)	1 (0.6)	0
Multiple races	0	0	1 (0.7)	0	0
Weight at baseline[b] (kg)	n = 156	n = 153	n = 141	n = 156	n = 140
Mean (SD)	87.6 (21.93)	87.6 (20.76)	83.1 (19.22)	89.5 (22.72)	87.0 (21.96)
Median	85.8	83.7	79.5	86.2	84.1
Min, max	45.0, 183.7	50.4, 160.1	43.9, 156.8	35.5, 172.4	46.9, 169.8
Acute S-K baseline, n (%)					
≤ 5.3 mmol/L	95 (60.1)	76 (49.4)	72 (51.1)	90 (57.3)	94 (65.7)
5.4-5.5 mmol/L	22 (13.9)	38 (24.7)	29 (20.6)	36 (22.9)	27 (18.9)
> 5.5 mmol/L	41 (25.9)	40 (26.0)	40 (28.4)	31 (19.7)	22 (15.4)
Acute eGFR at baseline, n (%)					
< 15 mL/min	15 (9.5)	8 (5.3)	15 (10.9)	8 (5.2)	10 (7.0)
15-29+ mL/min	44 (27.8)	42 (27.8)	38 (27.5)	43 (27.9)	42 (29.4)
30-59+ mL/min	61 (38.6)	73 (48.3)	48 (34.8)	64 (41.6)	50 (35.0)
≥ 60 mL/min	38 (24.1)	28 (18.5)	37 (26.8)	39 (25.3)	41 (28.7)
Etiology,[a] n (%)					
CKD	96 (60.8)	102 (66.2)	89 (63.1)	93 (59.2)	83 (58.0)
CHF	66 (41.8)	57 (37.0)	54 (38.3)	64 (40.8)	59 (41.3)
Diabetes mellitus	96 (60.8)	94 (61.0)	84 (59.6)	96 (61.1)	81 (56.6)
RAAS medication	101 (63.9)	109 (70.8)	97 (68.8)	99 (63.1)	96 (67.1)

(Source: ZS-003 Study Report p. 75)

A summary of demographics and other baseline characteristics for the subacute phase is presented by treatment group in Table 10 for the acute phase ZS subjects. The demographic and other baseline characteristics of the subacute phase ITT population were generally similar between treatment groups and also similar to the acute phase ITT population.

Table 10. Subacute Phase: Demographic and Other Baseline Characteristics – Acute Phase ZS Subjects - ITT [ZS-003]

Demographic Parameter Statistic	Acute Phase Treatment							
	ZS 1.25 g TID		ZS 2.5 g TID		ZS 5 g TID		ZS 10 g TID	
	Subacute Phase Treatment							
	Placebo (N = 41)	ZS QD (N = 49)	Placebo (N = 46)	ZS QD (N = 54)	Placebo (N = 68)	ZS QD (N = 64)	Placebo (N = 61)	ZS QD (N = 63)
Age at screening (years)								
Mean (SD)	66.9 (13.59)	62.3 (15.99)	65.8 (11.14)	67.1 (11.28)	65.0 (12.60)	64.6 (11.26)	66.8 (12.45)	65.5 (12.18)
Median	66.0	66.0	67.0	68.0	65.0	65.0	68.0	67.0
Min, max	22.0, 93.0	22.0, 85.0	35.0, 84.0	36.0, 91.0	24.0, 89.0	35.0, 86.0	33.0, 88.0	31.0, 91.0
Gender, n (%)								
Male	23 (56.1)	25 (51.0)	30 (65.2)	34 (63.0)	46 (67.6)	32 (50.0)	35 (57.4)	35 (55.6)
Female	18 (43.9)	24 (49.0)	16 (34.8)	20 (37.0)	22 (32.4)	32 (50.0)	26 (42.6)	28 (44.4)
Race,[a] n (%)								
White	37 (90.2)	44 (89.8)	39 (84.8)	49 (90.7)	54 (79.4)	56 (87.5)	48 (78.7)	55 (87.3)
Black or African American	4 (9.8)	3 (6.1)	3 (6.5)	5 (9.3)	10 (14.7)	7 (10.9)	9 (14.8)	8 (12.7)
Asian	0	0	3 (6.5)	0	2 (2.9)	1 (1.6)	2 (3.3)	0
American Indian or Alaska Native	0	0	0	0	1 (1.5)	0	1 (1.6)	0
Native Hawaiian or other Pacific Islander	0	2 (4.1)	0	0	0	0	1 (1.6)	0
Other	0	0	1 (2.2)	0	1 (1.5)	0	0	0

Table 10. (cont.) Subacute Phase: Demographic and Other Baseline Characteristics – Acute Phase ZS Subjects - ITT [ZS-003]

Weight at baseline[b] (kg)	n = 40	n = 48	n = 46	n = 54	n = 68	n = 63	n = 61	n = 61
Mean (SD)	84.5 (16.13)	82.9 (18.29)	85.8 (20.35)	81.3 (18.92)	93.9 (21.62)	87.1 (23.92)	86.7 (23.59)	89.8 (21.58)
Median	83.5	79.1	83.7	79.1	89.4	82.3	86.8	86.2
Min, max	56.7, 125.6	52.7, 127.9	55.0, 156.0	44.5, 136.2	55.1, 165.3	35.5, 172.7	47.4, 152.4	57.5, 170.9
Acute S-K baseline, n (%)								
≤ 5.3 mmol/L	29 (70.7)	27 (55.1)	32 (69.6)	31 (57.4)	38 (55.9)	42 (65.6)	41 (67.2)	39 (61.9)
5.4-5.5 mmol/L	9 (22.0)	12 (24.5)	8 (17.4)	15 (27.8)	17 (25.0)	14 (21.9)	13 (21.3)	12 (19.0)
> 5.5 mmol/L	3 (7.3)	10 (20.4)	6 (13.0)	8 (14.8)	13 (19.1)	8 (12.5)	7 (11.5)	12 (19.0)
Subacute S-K baseline, n (%)								
≤ 5.3 mmol/L	40 (97.6)	47 (95.9)	44 (95.7)	53 (98.1)	64 (94.1)	62 (96.9)	61 (100)	62 (98.4)
5.4-5.5 mmol/L	0	0	2 (4.3)	1 (1.9)	3 (4.4)	1 (1.6)	0	0
> 5.5 mmol/L	1 (2.4)	2 (4.1)	0	0	1 (1.5)	1 (1.6)	0	1 (1.6)
Acute eGFR at baseline, n (%)								
< 15 mL/min	1 (2.4)	2 (4.1)	4 (8.7)	5 (9.3)	3 (4.4)	5 (7.8)	6 (9.8)	3 (4.8)
15-29+ mL/min	14 (34.1)	7 (14.3)	12 (26.1)	14 (25.9)	19 (27.9)	20 (31.3)	18 (29.5)	22 (34.9)
30-59+ mL/min	16 (39.0)	29 (59.2)	15 (32.6)	17 (31.5)	32 (47.1)	21 (32.8)	21 (34.4)	23 (36.5)
≥ 60 mL/min	9 (22.0)	10 (20.4)	13 (28.3)	17 (31.5)	13 (19.1)	17 (26.6)	16 (26.2)	15 (23.8)
Subacute eGFR at baseline, n (%)								
< 15 mL/min	2 (4.9)	3 (6.1)	3 (6.5)	5 (9.3)	2 (2.9)	5 (7.8)	5 (8.2)	3 (4.8)
15-29+ mL/min	10 (24.4)	5 (10.2)	12 (26.1)	15 (27.8)	19 (27.9)	18 (28.1)	17 (27.9)	23 (36.5)
30-59+ mL/min	16 (39.0)	27 (55.1)	17 (37.0)	20 (37.0)	29 (42.6)	20 (31.3)	24 (39.3)	20 (31.7)
≥ 60 mL/min	12 (29.3)	14 (28.6)	10 (21.7)	14 (25.9)	17 (25.0)	19 (29.7)	15 (24.6)	17 (27.0)
Etiology,[a] n (%)								
CKD	25 (61.0)	32 (65.3)	26 (56.5)	33 (61.1)	42 (61.8)	37 (57.8)	36 (59.0)	37 (58.7)
CHF	12 (29.3)	14 (28.6)	15 (32.6)	22 (40.7)	28 (41.2)	26 (40.6)	23 (37.7)	26 (41.3)
Diabetes mellitus	23 (56.1)	27 (55.1)	27 (58.7)	30 (55.6)	48 (70.6)	36 (56.3)	37 (60.7)	36 (57.1)
RAAS medication	28 (68.3)	33 (67.3)	32 (69.6)	36 (66.7)	45 (66.2)	38 (59.4)	40 (65.6)	43 (68.3)

(Source: ZS-003 Study Report p. 77)

ZS-004

The 258 subjects enrolled in the acute phase of the study were treated with ZS 10 g TID. Of the 251 subjects who completed ZS 10 g TID dosing during the acute phase, 237 continued into the maintenance phase and were randomized to either placebo (85 subjects), ZS 5 g QD (45 subjects), ZS 10 g QD (51 subjects), or ZS 15 g QD (56 subjects) [Table 11, Table 12]. At enrollment into the Acute Phase, age ranged from 22 to 89 years, with a mean age of 64.0 years. The majority of the subjects were male (57.8%) and most were White (83.3%). The most common etiologies of elevated S-K (subjects could have had multiple etiologies) were use of

RAAS inhibitor medication (69.8%), CKD (based on eGFR < 60 mL/min, 69.4%), and diabetes mellitus (65.9%).

Table 11. Acute Phase: Subject Disposition – All Subjects [ZS-004]

Disposition, n (%)	ZS 10 g TID
Enrolled in Acute Phase	258
Treated	258 (100.0)
Completed Acute Phase	251 (97.3)
Discontinued Acute Phase	7 (2.7)
Consent withdrawn	5 (1.9)
Hyperkalemia	2 (0.8)

(Source: ZS-004 Study Report p. 81)

Table 12. Acute Phase: Subjects Who Did Not Enter Maintenance Phase By Reason – All Subjects [ZS-004]

Reason, n (%)	ZS 10 g TID (N = 258)
Did not complete Acute Phase	7 (2.7)
Completed Acute Phase	251 (97.3)
Ineligible to enter Maintenance Phase due to:	
Hypokalemia	2 (0.8)
Hyperkalemia	9 (3.5)
Eligible to enter Maintenance Phase	240 (93.0)
Eligible, but did not enter Maintenance Phase due to:	
Consent withdrawn	1 (0.4)
Investigator's decision	1 (0.4)[a]
Met ECG withdrawal criteria	1 (0.4)[b]
Entered Maintenance Phase	237 (91.9)

(Source: ZS-004 Study Report p. 82)

The majority of the subjects in each of the treatment groups completed the maintenance phase of the study (range: 86.3% to 88.9%) [Table 13].

Table 13. Maintenance Phase: Subject Disposition – All Subjects [ZS-004]

	Acute Phase Treatment: ZS 10 g TID			
	Maintenance Phase Treatment			
Disposition, n (%)	**Placebo**	**ZS 5 g QD**	**ZS 10 g QD**	**ZS 15 g QD**
Randomized	85	45	51	56
Treated	85 (100.0)	45 (100.0)	51 (100.0)	56 (100.0)
Completed Maintenance Phase	75 (88.2)	40 (88.9)	44 (86.3)	49 (87.5)
Discontinued Maintenance Phase	10 (11.8)	5 (11.1)	7 (13.7)	7 (12.5)
Adverse event	0 (0.0)	3 (6.7)	0 (0.0)	1 (1.8)
Consent withdrawn	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Subject compliance	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Investigator's decision	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)[a]
Sponsor's decision	2 (2.4)	0 (0.0)	2 (3.9)	1 (1.8)
Hypo- or hyperkalemia	3 (3.5)	0 (0.0)	3 (5.9)[b]	1 (1.8)
Met ECG withdrawal criteria	0 (0.0)	1 (2.2)	0 (0.0)	2 (3.6)
Other[c]	2 (2.4)	1 (2.2)	2 (3.9)	1 (1.8)

(Source: ZS-004 Study Report p. 84)

The demographic characteristics were generally similar among the maintenance phase treatment groups (Table 14). Among the treatment groups, mean age ranged from 61.5 to 64.9 years (overall range: 22 to 89 years). The majority of the subjects in each of the treatment groups were White (range: 80.0 to 86.3%). The proportions of male subjects tended to be higher in the ZS 15 q QD group (71.4%) compared with the placebo (51.8%) and the lower ZS dose (5 g QD: 60.0%; 10 g QD: 52.9%) groups. Greater proportions of subjects in the ZS 15 g QD group had HF, CKD (based on eGFR < 60 mL/min) and diabetes mellitus compared with the placebo group.

Table 14. Maintenance Phase: Demographic and Other Baseline Characteristics – Safety Population [ZS-004]

Demographic Parameter Statistic	Acute Phase Treatment: ZS 10 g TID Maintenance Phase Treatment Placebo (N = 85)	ZS 5 g QD (N = 45)	ZS 10 g QD (N = 51)	ZS 15 g QD (N = 56)
Age at screening (years)				
Mean (SD)	64.3 (12.13)	61.5 (16.89)	63.8 (9.97)	64.9 (12.85)
Median	66.0	64.0	65.0	64.5
Min, max	23, 87	22, 89	44, 85	25, 85
Gender, n (%)				
Male	44 (51.8)	27 (60.0)	27 (52.9)	40 (71.4)
Female	41 (48.2)	18 (40.0)	24 (47.1)	16 (28.6)
Race,[a] n (%)				
White	73 (85.9)	36 (80.0)	44 (86.3)	46 (82.1)
Black or African American	10 (11.8)	8 (17.8)	5 (9.8)	9 (16.1)
Asian	3 (3.5)	0 (0.0)	1 (2.0)	1 (1.8)
Native Hawaiian or other Pacific Islander	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (2.2)	1 (2.0)	0 (0.0)
Multiple races indicated	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, n (%)				
Hispanic	38 (44.7)	19 (42.2)	23 (45.1)	21 (37.5)
Not Hispanic	47 (55.3)	26 (57.8)	28 (54.9)	35 (62.5)
Weight at baseline[b] (kg)	n = 85	n = 45	n = 51	n = 55
Mean (SD)	85.12 (18.575)	89.57 (23.907)	87.38 (25.616)	87.17 (18.627)
Median	84.30	87.30	84.40	84.50
Min, max	52.0, 134.5	53.5, 185.4	46.2, 175.2	44.5, 137.8
Acute Phase S-K baseline, n (%)				
< 5.5 mmol/L	43 (50.6)	23 (51.1)	19 (37.3)	24 (42.9)
5.5 - < 6.0 mmol/L	30 (35.3)	17 (37.8)	23 (45.1)	26 (46.4)
≥ 6.0 mmol/L	12 (14.1)	5 (11.1)	9 (17.6)	6 (10.7)
Acute Phase eGFR at baseline, n (%)				
< 60 mL/min	52 (61.2)	31 (68.9)	38 (74.5)	41 (73.2)
≥ 60 mL/min	28 (32.9)	12 (26.7)	13 (25.5)	15 (26.8)
Missing	5 (5.9)	2 (4.4)	0 (0.0)	0 (0.0)
Etiology,[a] n (%)				
RAAS inhibitor medication	61 (71.8)	33 (73.3)	36 (70.6)	33 (58.9)
Diabetes mellitus	54 (63.5)	26 (57.8)	38 (74.5)	39 (69.6)
CKD	50 (58.8)	29 (64.4)	36 (70.6)	37 (66.1)
HF	26 (30.6)	18 (40.0)	18 (35.3)	25 (44.6)

(Source: ZS-004 Study Report, p. 90-91)

3.2.4 Results and Conclusions

An overview of the sponsor's primary efficacy results is provided in Table 15.

Table 15. Primary Efficacy Results Overview

	Acute	Subacute
ZS-002	Exponential rate of change (48 h) ZS 0.3 g: p = 0.4198 **ZS 3.0 g: p = 0.0480** **ZS 10 g: p < 0.0001**	-
ZS-003	Exponential rate of change (48 h) ZS 1.25 g: p = 0.5037 **ZS 2.5 g: p = 0.0009** **ZS 5 g: p < 0.0001** **ZS 10 g: p < 0.0001**	Exponential rate of change (12 days) ZS 1.25 g: p = 0.4252 ZS 2.5 g: p = 0.8396 **ZS 5 g: p = 0.0083** **ZS 10 g: p < 0.0001**
ZS-004	-	LS Mean (Days 8 to 29) Placebo: 5.06 **ZS 5 g: 4.75 (p = 0.0001)** **ZS 10 g: 4.51 (p < 0.0001)** **ZS 15 g: 4.37 (p < 0.0001)**

(Source: Compiled by Reviewer from Study Reports; bold font doses are statistically significant)

ZS-002

Efficacy Results

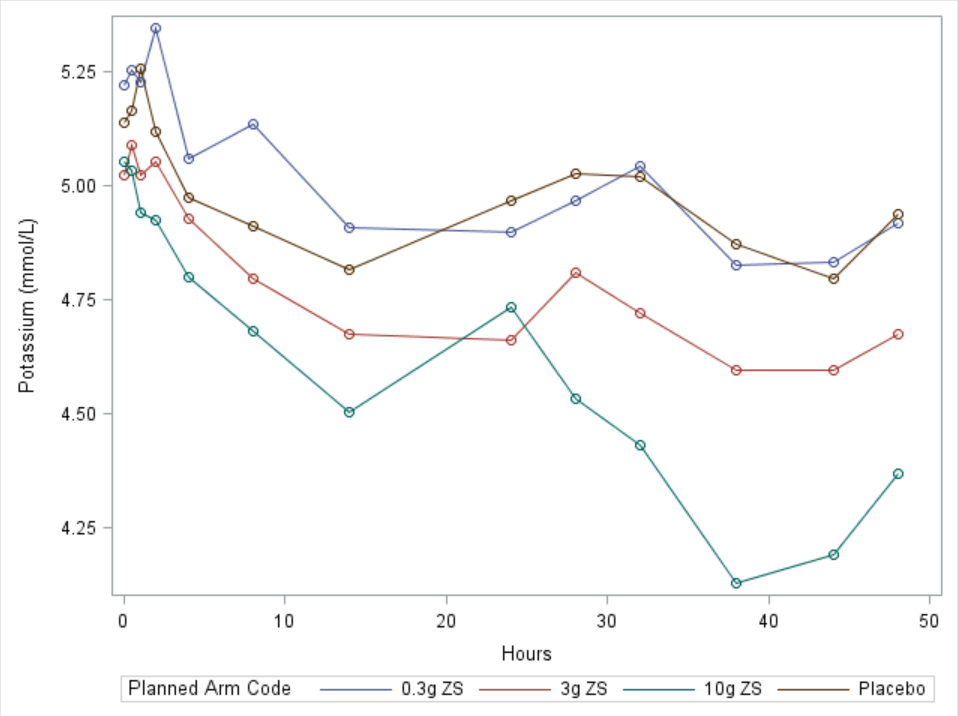
The sponsor states that ZS resulted in statistically significant dose-dependent reductions in S-K in subjects with hyperkalemia and met the predefined primary endpoint of exponential decrease in S-K from baseline to 48 hours at the 10 g TID dose ($p < 0.0001$) as well as the 3 g TID dose ($p = 0.048$). ZS at the 3 g TID and 10 g TID doses resulted in mean maximal reductions of 0.43 mmol/L and 0.92 mmol/L, respectively.

Table 16. Statistical Model of Serum Potassium (mmol/L) Exponential Rate of Change to 24 Hours and 48 Hours – ITT [ZS-002]

	Solution for Fixed Effects						
Endpoint	**Effect**	**Dose (g) TID**	**Estimate[a]**	**Standard error**	**DF**	**t-Value**	**Pr > |t|**
24 Hours	Intercept		1.61766	0.008414	89	192.25	< 0.0001
	Time		-0.00228	0.000633	86	-3.60	0.0005
	Time*Dose	ZS 0.3	-0.00035	0.001166	86	-0.30	0.7661
	Time*Dose	ZS 3.0	-0.00169	0.000932	86	-1.81	0.0737
	Time*Dose	ZS 10	-0.00143	0.000932	86	-1.53	0.1293
	Time*Dose	Placebo	0				
48 Hours	Intercept		1.61196	0.008095	89	199.13	< 0.0001
	Time		-0.00096	0.000298	86	-3.21	0.0019
	Time*Dose	ZS 0.3	-0.00045	0.000555	86	-0.81	0.4198
	Time*Dose	ZS 3.0	-0.00089	0.000444	86	-2.01	0.0480
	Time*Dose	ZS 10	-0.00256	0.000444	86	-5.77	< 0.0001
	Time*Dose	Placebo	0				

(Source: ZS-002 Study Report p. 53; Results confirmed by reviewer)

Figure 1. Mean Serum Potassium Over Initial 48 Hours – ITT [ZS-002]



(Source: Reviewer; SAS code: Prim_Anal_ZS002)

ZS-003

The sponsor's summary of the primary efficacy results is provided in Table 17.

Table 17. Closed Testing Procedure and the Exponential Rate of Change in Serum Potassium During the Acute and Subacute Phases [ZS-003]

Treatment Group	Exponential Decrease in S-K p-value
Acute Phase: ZS 10 g TID versus placebo TID	10^{-31}
Subacute Phase: ZS 10 g QD versus corresponding placebo QD	10^{-23}
Acute Phase: ZS 5 g TID versus placebo TID	< 0.0001
Subacute Phase: ZS 5 g QD versus corresponding placebo QD	0.0083
Acute Phase: ZS 2.5 g TID versus placebo TID	0.0009
Subacute Phase: ZS 2.5 g QD versus corresponding placebo QD	Not significant (p = 0.4761)
Acute Phase: ZS 1.25 g TID versus placebo TID	Not significant (p = 0.0874)
Subacute Phase: ZS 1.25 g QD versus corresponding placebo QD	Not significant (p = 0.1900)

(Source: ZS-003 Study Report p. 80)

Some of the p-values in the sponsor's table above were not taken from the correct output tables. Table 18 below provides the correct results. This correction does not change any of the sponsor's conclusions. Also, all digits were maintained to allow for an easier comparison of both tables.

Table 18. Correct P-values for Primary Endpoint in Acute and Subacute Phases [ZS-003]

ZS Treatment Group	P-value for comparison to placebo	
	Acute Phase	Subacute Phase
10 g	< 0.0001	< 0.0001
5 g	< 0.0001	0.0083
2.5 g	0.0009	0.8396 [~~0.4761~~]
1.25 g	0.5037 [~~0.0874~~]	0.4252 [~~0.1900~~]

(Source: Table 14.2.2A; Tables 14.2.2.1S - 14.2.2.4S; Values are corrected compared to Table 11-7 in ZS-03 Study Report [24 hour instead of 48 hour p-value was displayed for 1.25 g acute dose; Day 8 instead of Day 15 p-values were displayed for subacute phase for 2.5 and 1.25 g doses]; Results confirmed by reviewer)

Table 19 provides the rate of change estimates for both study phases.

Table 19. Estimates of Exponential Rates of Change [ZS-003]

ZS Treatment Group	Acute Phase (48 hours)	Subacute Phase (12 days)
10 g	-0.00224	-0.00844
5 g	-0.00127	-0.00368
2.5 g	-0.00066	0.00031
1.25 g	-0.00013	0.00113

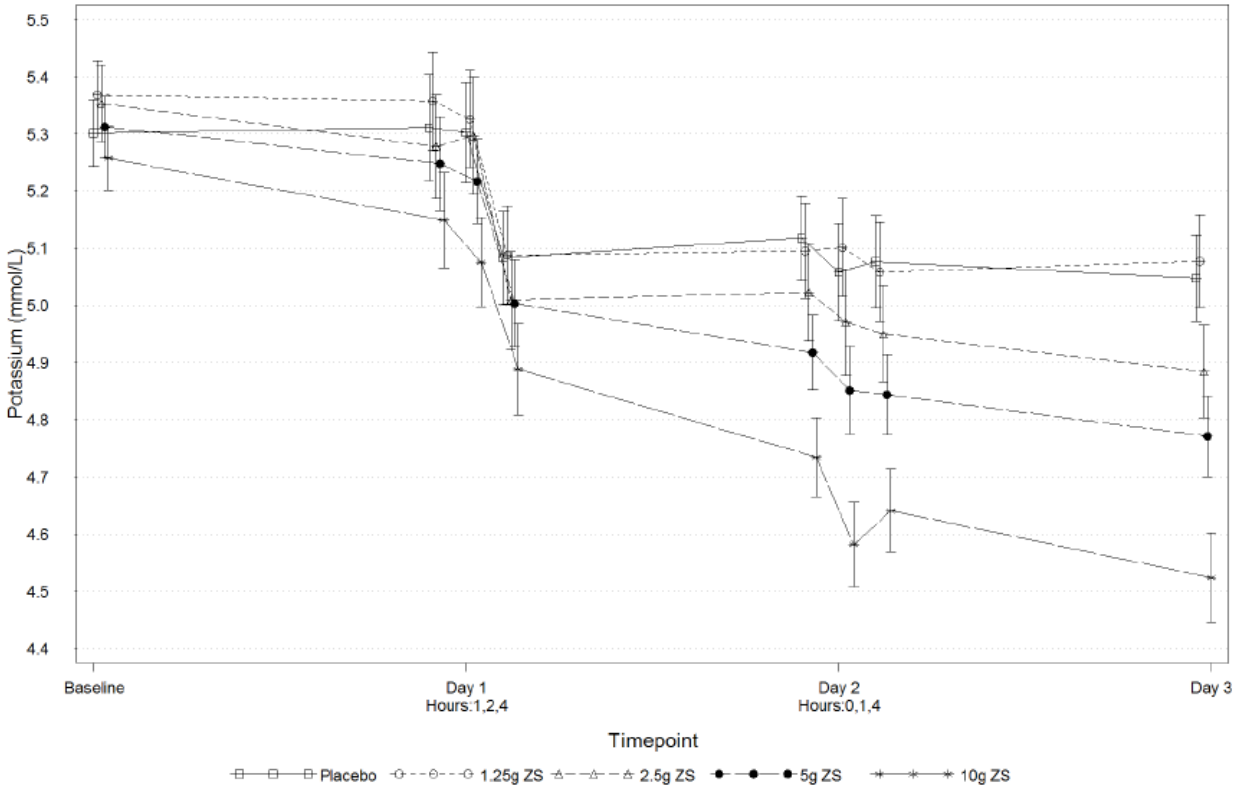
(Source: Tables 14.2.2.1S and 14.2.2A in ZS-003 Study Report; Estimates of time by treatment interaction with Placebo as reference [i.e., Placebo by time interaction coefficient is fixed as 0)

Secondary Endpoints

The secondary efficacy endpoints for the Acute Phase included mean change (absolute and percent) from baseline in S-K values, time to a decrease in S-K values of 0.5 mmol/L, time to normalization in S-K values, and percentage of subjects who were normokalemic at 48 hours. No multiple comparison control procedure was pre-specified for the secondary endpoints.

However, since the interpretation of the rate estimates (primary endpoint) is not that intuitive the figure below is included which provides the serum potassium means (secondary endpoint) over the course of the acute phase.

Figure 2. Acute Phase: Mean Serum Potassium Over Initial 48 Hours – ITT [ZS-003]



(Source: ZS-003 Study Report p. 81; Mean (± 2 × Standard Error))

ZS-004

Open-label Acute Phase

The sponsor states that ZS was highly effective in reducing S-K in subjects with hyperkalemia, demonstrating statistically significant improvement from baseline in S-K with ZS 10 g TID over the first 48 hours of dosing.

Maintenance Phase

Subjects who achieved normokalemia after receiving ZS 10 g TID in the acute phase were randomized to 28 days of placebo, ZS 5 g QD, ZS 10 g QD, or ZS 15 g QD dosing during the maintenance phase. Each ZS group had a statistically significantly smaller mean S-K value than the placebo group ($p \leq 0.001$ for each ZS dose group) during maintenance phase Study Days 8 to 29. The mean S-K value decreased with increasing dose of ZS (5.1 mmol/L for placebo, 4.8 mmol/L for ZS 5 g QD, 4.5 mmol/L for ZS 10 g QD, and 4.4 mmol/L for ZS 15 g QD) [Table 20].

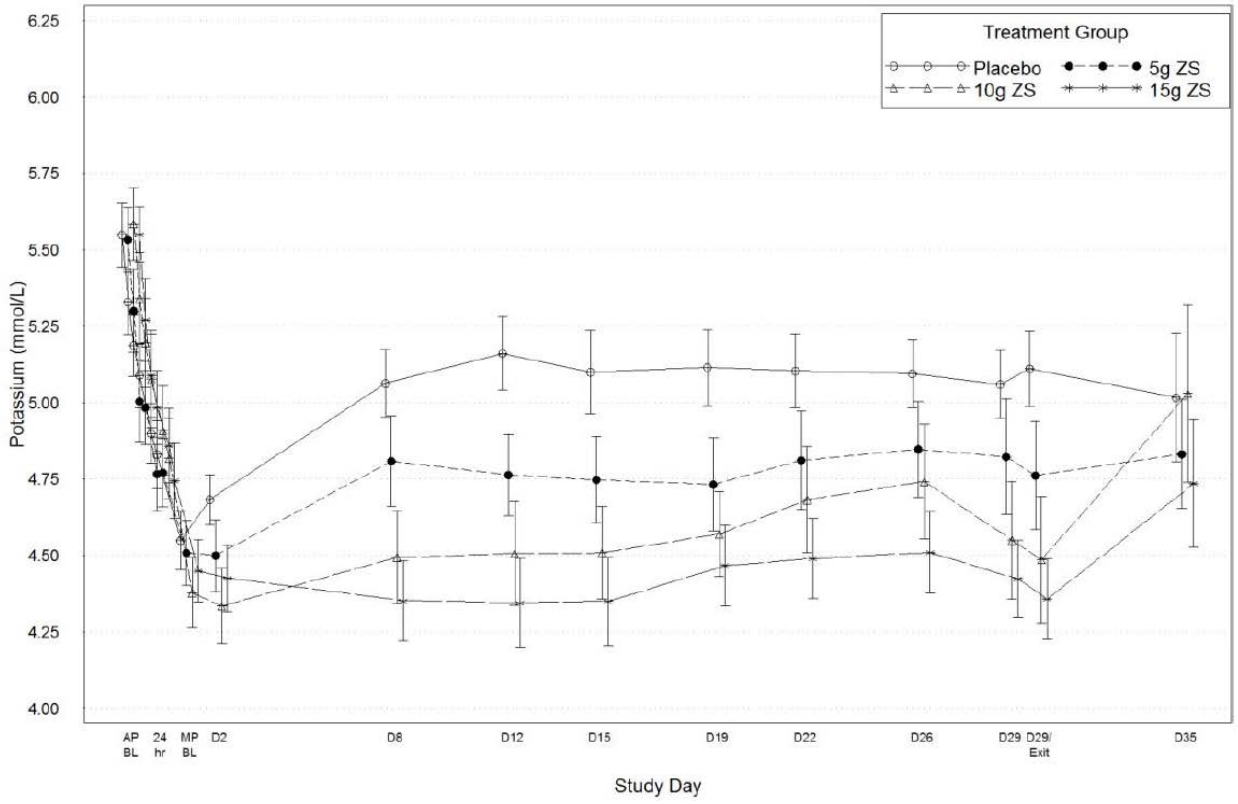
Table 20. Maintenance Phase: LS Mean Serum Potassium Between Maintenance Phase Study Days 8 and 29 – ITT [ZS-004]

Statistic[a]	Acute Phase Treatment: ZS 10 g TID Maintenance Phase Treatment Placebo (N = 82)	ZS 5 g QD (N = 45)	ZS 10 g QD (N = 50)	ZS 15 g QD (N = 54)
Back-transformed from model				
Least squares mean	5.0603	4.7544	4.5081	4.3742
95% confidence interval	4.9646, 5.1578	4.6350, 4.8769	4.4005, 4.6184	4.2754, 4.4753
Log-transformed (as modelled)				
Least squares mean (standard error)	1.6214 (0.009681)	1.5591 (0.012906)	1.5059 (0.012260)	1.4757 (0.011595)
95% confidence interval	1.6023, 1.6405	1.5336, 1.5845	1.4817, 1.5300	1.4529, 1.4986
t-test p-value (ZS versus placebo)		0.0001	< 0.0001	< 0.0001

(Source: ZS-004 Study Report p. 103; Results confirmed by reviewer)

Figure 3 provides a display of mean serum potassium levels over the course of the maintenance phase.

Figure 3. Maintenance Phase: Mean Serum Potassium over Time – ITT [ZS-004]



(Source: ZS-004 Study Report p. 104)

Secondary Endpoints

Based on the sequential closed testing procedure, each ZS dose group was superior to placebo for the predefined secondary efficacy endpoints of total number of days normokalemic and proportion of subjects normokalemic on maintenance phase Study Day 29/Exit. A statistically significantly greater number of normokalemic days were observed for each ZS group versus placebo. The mean number of normokalemic days increased with increasing dose of ZS (7.4/22 days for placebo, 13.4/22 days for ZS 5 g QD, 13.9/22 days for ZS 10 g QD, and 16.8/22 days for ZS 15 g QD). At maintenance phase Study Day 29/Exit, the proportion of subjects who remained normokalemic was statistically significantly larger in the ZS 5 g QD, ZS 10 g QD, and ZS 15 g QD groups (71.1%, 76.0%, and 85.2% of subjects, respectively) than in the placebo group (47.6% of subjects).

Table 21. Maintenance Phase: Secondary Endpoints [ZS-004]

	ZS 15 g	**ZS 10 g**	**ZS 5 g**
Total number of days normokalemic	Stat sign	Stat sign	Stat sign
Day 29 proportion of subjects normokalemic	Stat sign	Stat sign	Stat sign
Mean S-K intra-subject standard deviation	Not stat sign	-	-

(Exponential rate of change in S-K in open-label acute phase was stat sign for all three doses; Compare to Table 11-7 in CSR; Results confirmed by reviewer)

The effectiveness of ZS in maintaining normokalemia in subjects with initial hyperkalemia was also illustrated by mean changes from the acute phase and maintenance phase baselines. Mean change from the Acute Phase baseline to Maintenance Phase Study Day 29/Exit was -0.44 mmol/L in the placebo group, -0.77 mmol/L in the ZS 5 g QD group, -1.10 mmol/L in the ZS 10 g QD group, and -1.19 mmol/L in the ZS 15 g QD group. Mean change from the maintenance phase baseline to maintenance phase Study Day 29/Exit was 0.56 mmol/L in the placebo group, 0.25 mmol/L in the ZS 5 g QD group, 0.11 mmol/L in the ZS 10 g QD group, and -0.09 mmol/L in the ZS 15 g QD group.

Reviewer's results

Primary endpoints

This reviewer was able to replicate the primary efficacy analyses results for the primary endpoints (exponential rate of change in ZS-002 and ZS-003; LS Mean for ZS-004).

Secondary endpoints

This reviewer also replicated the results for the key secondary endpoints in Study ZS-004.

Pre-specified Multiple Comparison Procedures?

This section provides a summary about which trial (and which phase of each respective trial) had a pre-specified multiple comparison procedure. There are no issues for the primary endpoints in any of the three studies reviewed; however Study ZS-003 lacks a pre-specified testing procedure to control the overall type I error rate for the secondary endpoints.

ZS 002

Primary endpoint: Exponential rate of change in S-K levels during initial 48 hours

Closed testing procedure: from highest to lowest dose (10, 3, 0.3 g) [SAP p. 27];

All other endpoints are exploratory (no multiple comparison procedure [MCP]).

ZS 003

Primary endpoint: Exponential rate of change

Closed testing procedure: from highest to lowest dose (10, 5, 2.5, 1.25 g) and within each dose level acute phase first and subacute phase second [SAP p. 33-34]

Secondary endpoints:

SAP p. 36/37 (Note: protocol has no additional info re MCP)

The sponsor refers to "a closed testing procedure … as previously detailed" when describing the secondary efficacy endpoints in the SAP, but the only previously detailed MCP outlines the approach for the primary endpoint. The sponsor did not specify an order in which the different secondary endpoints would be tested, even if we assumed a similar process as for the primary endpoint (i.e., acute before subacute phase and from highest to lowest dose level).

Statements from the SAP:

Acute Phase: "Secondary efficacy endpoints will include S-K at all time points, time to normalization of S-K […], time to first decrease in S-K of 0.5 mmol/l, and proportion of subjects who achieve normalization in S-K levels at the end of 24 and 48 hours" (SAP p.36).

Subacute Phase: " … maintaining normokalemic control […], time to a 0.5 mmol/l increase, and time to relapse […], which will serve as the lead secondary efficacy endpoints" (SAP p. 37).

Due to this lack of pre-specification of a testing order the overall type I error is not controlled for the numerous secondary endpoints in Study ZS-003 and they can only be considered exploratory. A listing of those secondary endpoints and whether they were nominally statistical significant is provided in the appendix.

ZS 004

Primary endpoint: LS mean of all available S-K values in maintenance phase Days 8-29;

Sequential closed testing procedure: highest to lowest dose (15, 10, 5 g) [SAP p. 13]

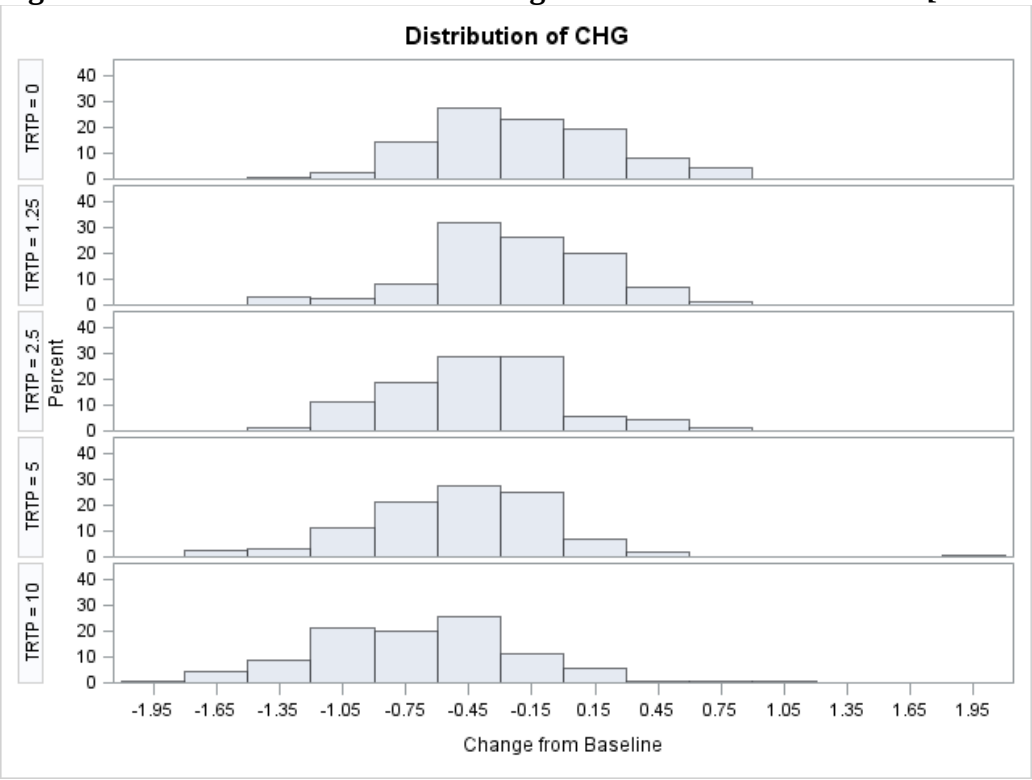
Secondary endpoints:

Sequential closed testing procedure [SAP p. 13-14]

1) Acute phase: S-K exponential rate of change;
2) [Primary endpoint];
3) Maintenance Phase: total number of days normokalemic (from highest to lowest dose);
4) Maintenance Phase: Day 29 proportion of subjects normokalemic (from highest to lowest dose);
5) Maintenance Phase: Mean S-K intra-subject standard deviation (from highest to lowest dose).

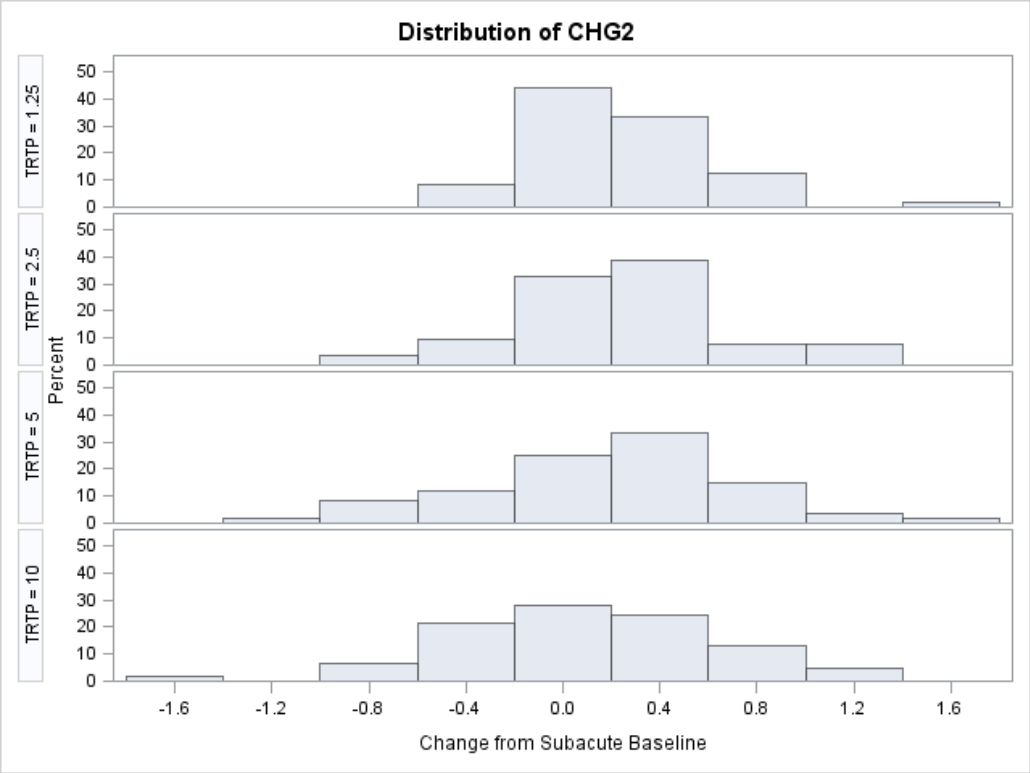
Below are several histograms (created per clinical request) displaying the change in potassium levels separately for the acute and subacute phases by dose level.

Figure 4. Acute Phase Potassium Change from Baseline at 48 hours [ZS-003]



[Source: Reviewer (SAS code: Potas_Histogram_Z003)]

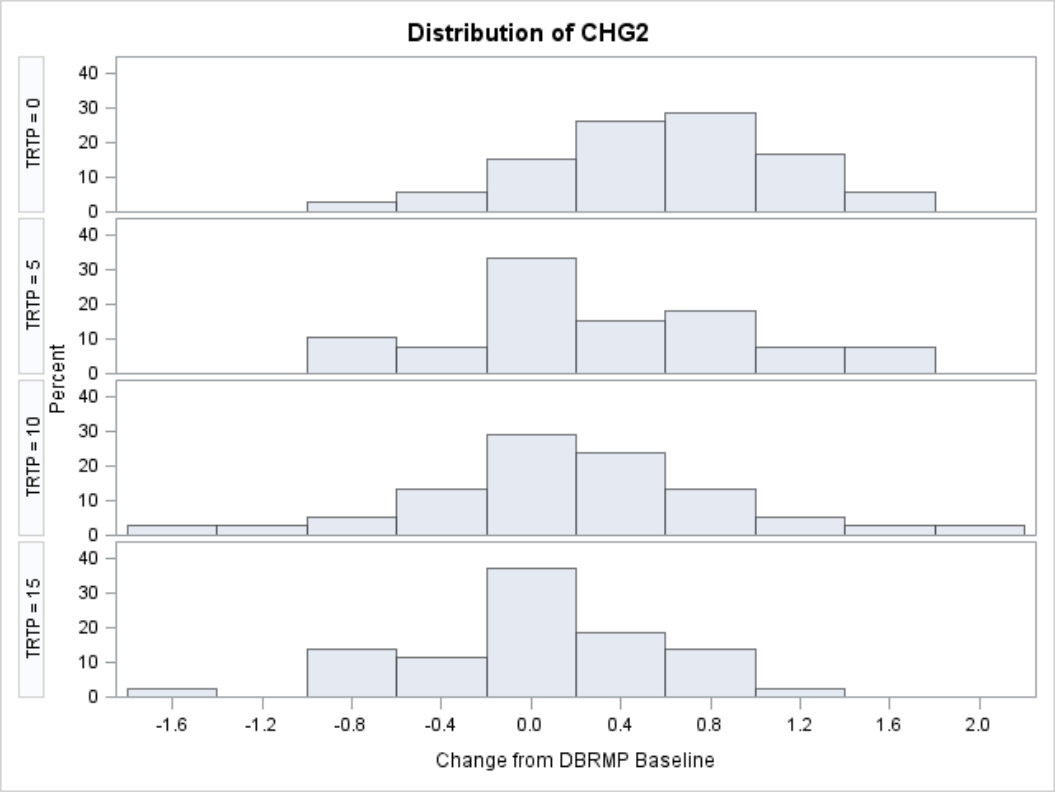
Figure 5. Subacute Phase Potassium Change from Baseline (Day 3) to Day 15 [ZS-003]



[Source: Reviewer (SAS code: Potas_Histogram_Z003)]

ZS-004

Figure 6. Potassium Change from Maintenance Phase Baseline (Day 3) to Day 29 [ZS-004]



[Source: Reviewer (SAS code: Potas_Histogram_Z004)]

3.3 Evaluation of Safety

The reader is referred to the clinical review for the evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

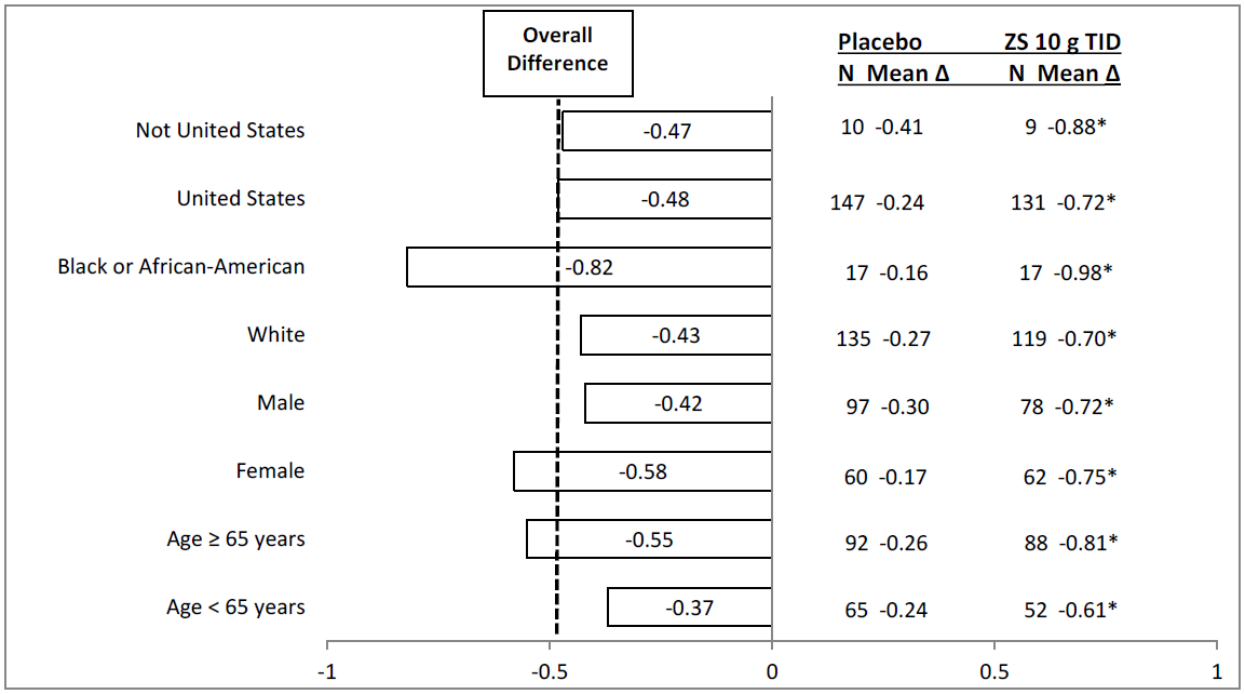
4.1 Gender, Race, Age, and Geographic Region

ZS-003 Acute Phase Demographic Subgroups

Treatment differences between the ZS 10 g TID and placebo groups for mean change in S-K from baseline to 48 hours are summarized by demographic subgroups in Figure 7. The ZS 10 g TID group had larger mean decreases than the placebo group in all demographic subpopulations. The somewhat larger difference observed for Black subjects might be due to the relatively small

sample size (n = 17 each) in that subgroup. Consistent results among demographic subgroups favoring ZS over placebo were also obtained for the ZS 5 g TID subjects.

Figure 7. Treatment Differences Between the ZS 10 g TID and Placebo Groups for Mean Change in Serum Potassium (mmol/L) from Baseline to 48 Hours by Demographic Characteristics – ITT [ZS-003]

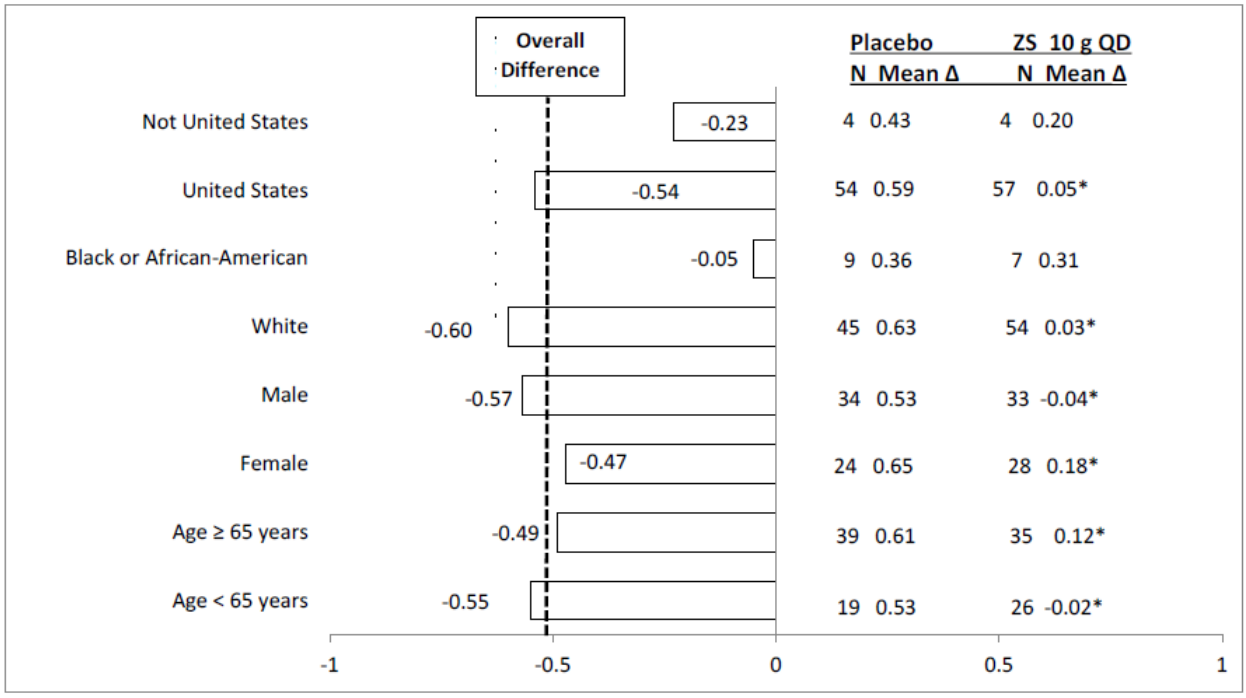


(Source: Summary of Clinical Efficacy p. 55; * = Nominally statistically significant ($p \leq 0.05$) versus placebo based on t-test)

ZS-003 Subacute Phase Demographic Subgroups

Treatment differences between the ZS 10 g QD and placebo groups for mean change in S-K from extended dosing baseline to extended dosing Study Day 12 are summarized by demographic characteristics in Figure 8. The ZS 10 g QD group had smaller mean increases than the placebo group in all subpopulations.

Figure 8. Treatment Differences Between the ZS 10 g TID and Placebo Groups for Mean Change in Serum Potassium (mmol/L) from Extended Dosing Baseline to Study Day 12 by Demographic Characteristics – ITT [ZS-003]



(Source: Summary of Clinical Efficacy p. 60; * = Nominally statistically significant ($p \leq 0.05$) versus placebo based on t-test)

ZS-003 Subgroup Analysis of Lot #5567-17613-A

Note that when Study ZS-003 was initiated, the study drug was supplied using the manufacturing process current at that time. However, (b) (4) the process were finalized near the end of enrollment of Study ZS-003. As this process is representative of the intended commercial manufacturing process, the sponsor decided to dose the remaining subjects enrolled in Study ZS-003 with ZS manufactured using this process. Of the 37 subjects in the subgroup population who were treated with ZS from Lot #5567-17613-A during the acute phase, 27 continued into the

subacute phase and were randomized either to continue on the same ZS dose administered QD or to placebo.

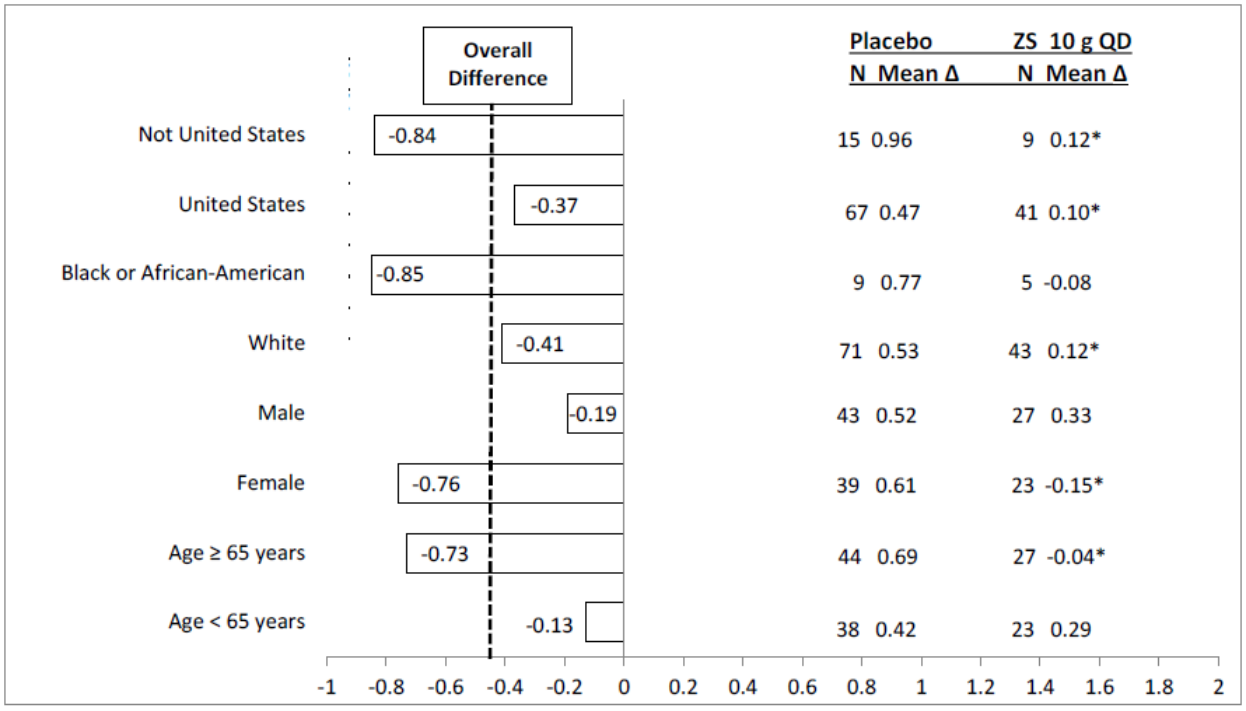
Efficacy and safety results observed for subjects who received ZS from Lot #5567-17613-A (subgroup population) were consistent with those observed in the overall population for both the acute and subacute phases of the study.

A separate study report presents efficacy and safety data from the subgroup of subjects who received ZS from the initial commercial manufacturing batch (Lot #5567-17613-A), which represents approximately 6% of all ZS-treated subjects during the Acute Phase of Study ZS-003.

ZS-004 Maintenance Phase

The ZS 10 g QD group had smaller mean increases in serum potassium than the placebo group in all subgroups (Figure 9).

Figure 9. Treatment Differences Between the ZS 10 g TID and Placebo Groups for Mean Change in Serum Potassium (mmol/L) from Extended Dosing Baseline to Study Day 29 by Demographic Characteristics – ITT [ZS-004]



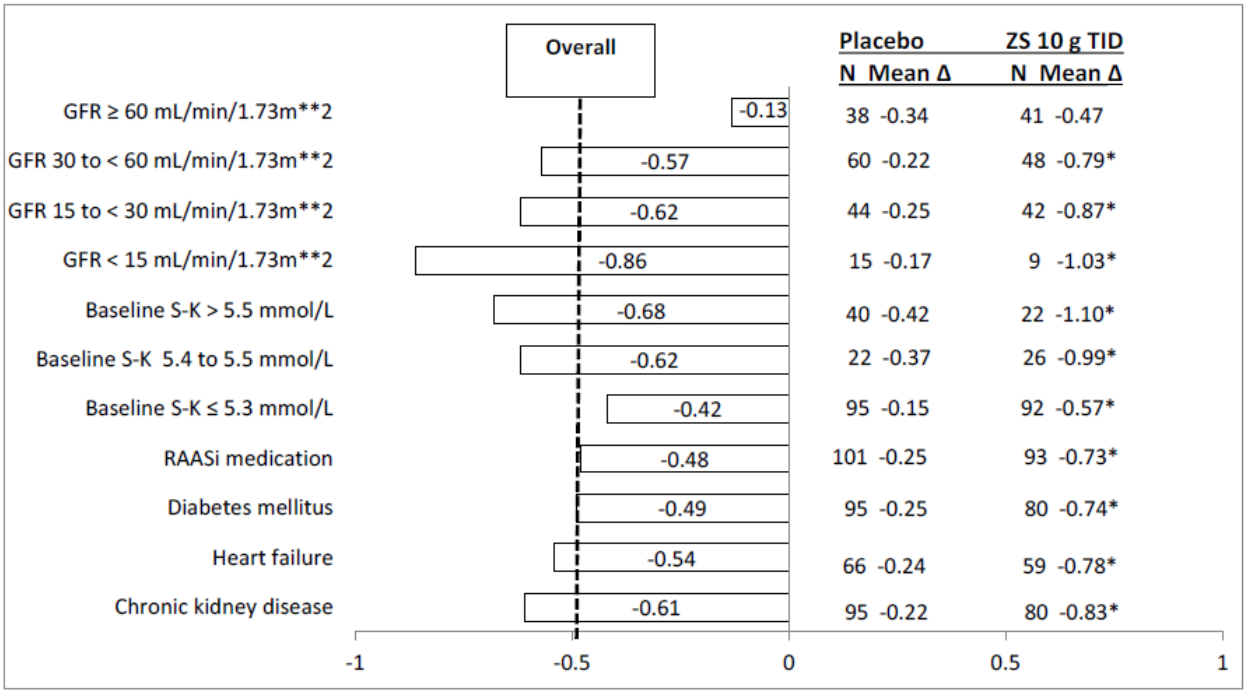
(Source: Summary of Clinical Efficacy p. 64; * = Nominally statistically significant ($p \leq 0.05$) versus placebo based on t-test)

4.2 Other Special/Subgroup Populations

ZS-003 Acute Phase Subgroups based on Baseline Characteristics

Treatment differences between the ZS 10 g TID and placebo groups for mean change in S-K from baseline to 48 hours are summarized by baseline characteristics (i.e., eGFR, S-K, Concomitant Diseases, and Use of RAAS Inhibitor Medication) in Figure 10. The ZS 10 g TID group had larger mean decreases than the placebo group in all subgroups. The mean reduction at 48 hours in the ZS 10 g TID group increased with higher baseline S-K values and with lower baseline eGFR values.

Figure 10. Treatment Differences Between the ZS 10 g TID and Placebo Groups for Mean Change in Serum Potassium (mmol/L) from Baseline to 48 Hours by Baseline Characteristics – ITT [ZS-003]

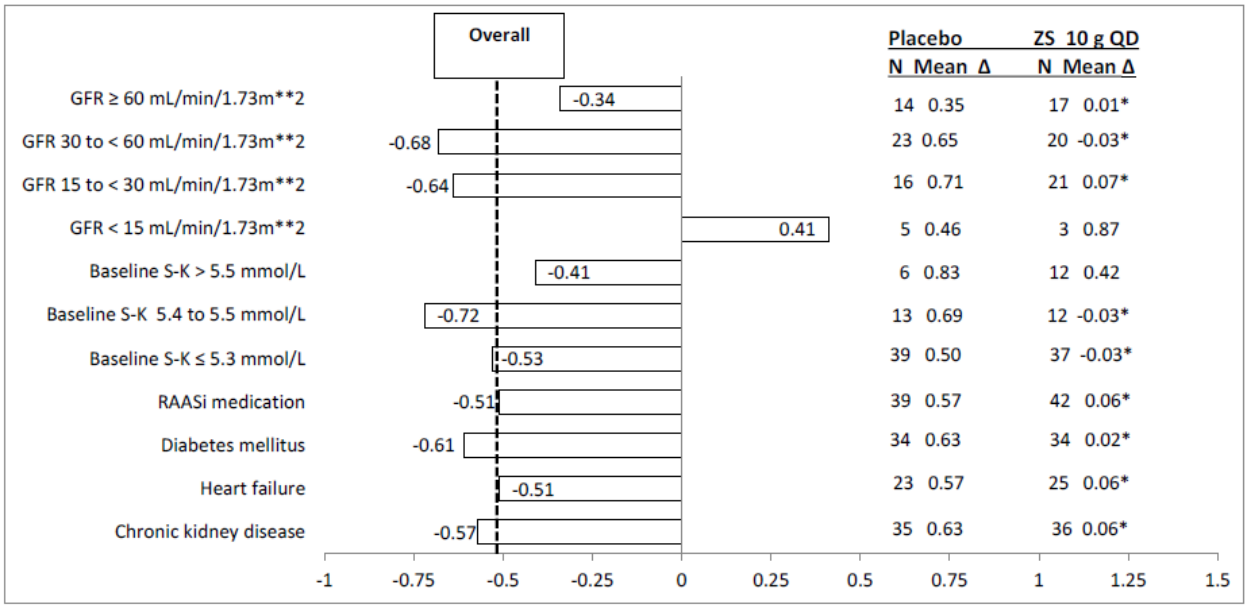


(Source: Summary of Clinical Efficacy p. 56; * = Nominally statistically significant ($p \leq 0.05$) versus placebo based on t-test)

ZS-003 Subacute Phase Subgroups based on Baseline Characteristics

The ZS 10 g QD group had smaller mean increases than the placebo group in all subpopulations, expect for the very small subgroups with the lowest GFR measurements (Figure 11).

Figure 11. Treatment Differences Between the ZS 10 g QD and Placebo Groups for Mean Change in Serum Potassium (mmol/L) from Subacute Phase Baseline to Study Day 12 by Baseline Characteristics – ITT [ZS-003]

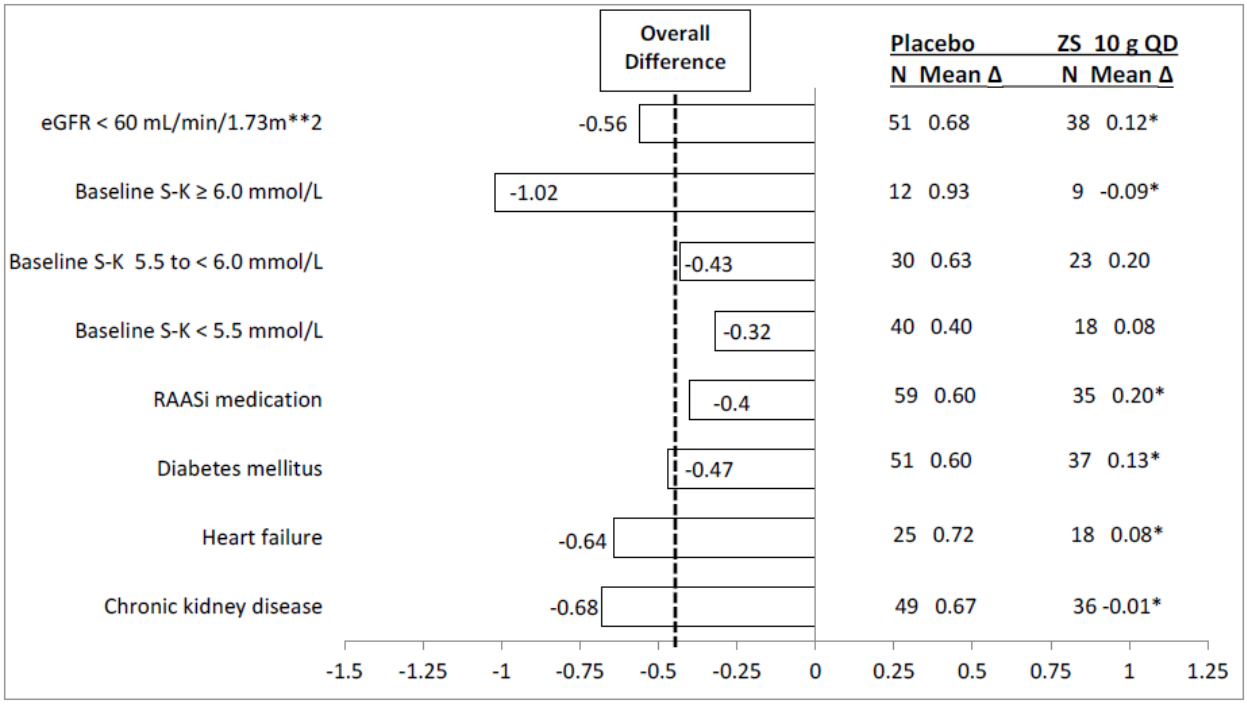


(Source: Summary of Clinical Efficacy p. 62; * = Nominally statistically significant ($p \leq 0.05$) versus placebo based on t-test)

ZS-004 Maintenance Phase

Treatment differences between the ZS 10 g group and the placebo group for mean change in S-K from maintenance phase baseline to Day 29 are summarized in Figure 12 and appear consistent across subpopulations.

Figure 12. Treatment Differences Between the ZS 10 g QD and Placebo Groups for Mean Change in Serum Potassium (mmol/L) from Extended Dosing Baseline to Study Day 29 by Baseline Characteristics – ITT [ZS-004]



(Source: Summary of Clinical Efficacy p. 67; * = Nominally statistically significant ($p \leq 0.05$) versus placebo based on t-test)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No multiple comparison procedure was pre-specified for the secondary endpoints in Study ZS-003. The overall type I error was not controlled and analysis for the secondary endpoints in Study ZS-003 can only be viewed as exploratory.

5.2 Collective Evidence

Efficacy was demonstrated by the primary efficacy endpoints (exponential rate of change in SK for Studies ZS-002 [acute phase at doses of 3g and 10g] and ZS-003 [acute and subacute phases at doses of 5g and 10g]; LS Mean over duration of maintenance phase at doses of 5, 10 and 15 g ZS in Study ZS-004). Study ZS-004 provided further support of efficacy by means of statistically

significant differences to placebo in the secondary endpoints of ‘total number of days normokalemic’ and ‘proportion of subjects normokalemic at day 29’ for all three ZS doses tested.

5.3 Conclusions and Recommendations

The statistical results provide adequate evidence to support an efficacy claim of ZS at the 5, 10, and 15 g doses administered three times a day during the first 48 hours in lowering potassium levels and once a day for up to month to maintain those lower levels. Note that the ZS 15 mg dose was included only in Study ZS-004.

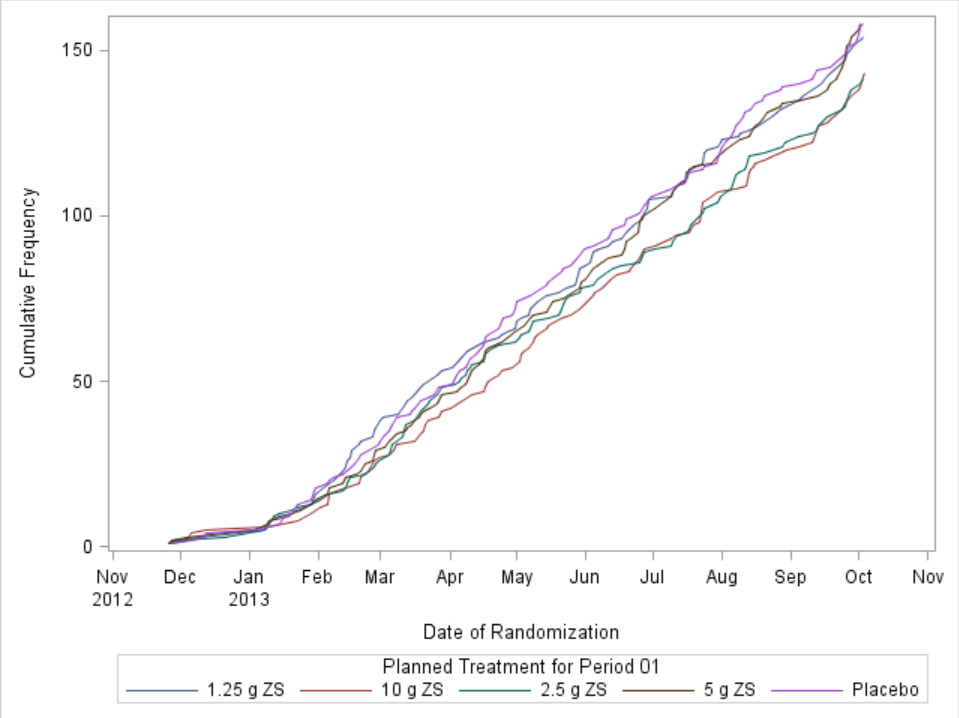
5.4 Labeling Recommendations

(b) (4)

The presentation of results for the open label acute phase in Study ZS-004 should be minimized.

APPENDICES

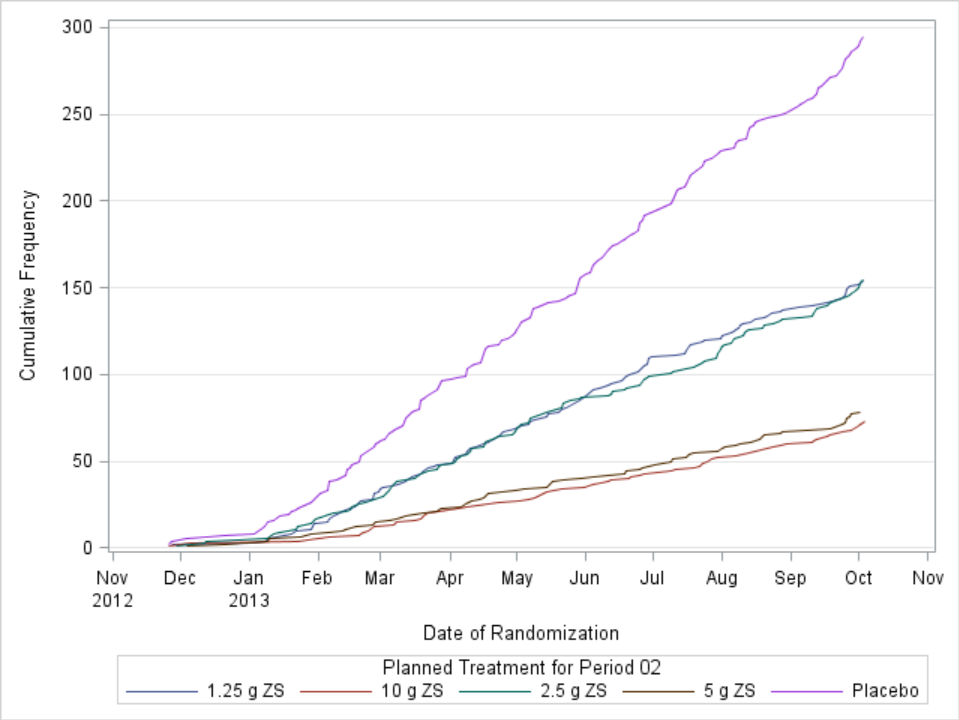
Figure A1. ZS-003 Randomization to Acute Phase



(Source: Reviewer)

Note: 2.5 and 10 mg doses separate somewhat from the other dose groups (fewer subjects are randomized to those two groups).

Figure A2. ZS-003 Randomization to Subacute Phase (Planned)



(Source: Reviewer)

Patients were randomized to acute and subacute phase treatment at the same time. However, only subjects with S-K between 3.5 to 5.0 mmol/L at the end of the acute phase qualified for the subacute phase (i.e., realized their subacute phase treatment assignment). The figure above displays the treatment assignments in theory, disregarding the normokalemia condition to continue into the subacute phase.

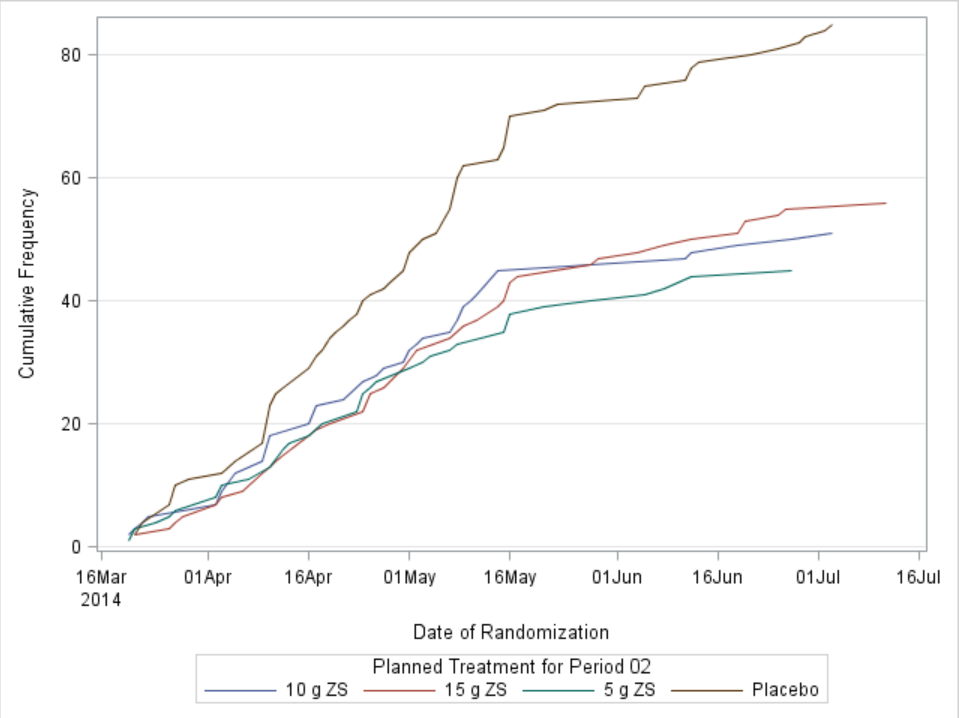
Table A1. ZS-003 Randomization (Acute and Subacute treatment sequence)

Description of Planned Arm				
ARM	**Frequency**	**Percent**	**Cumulative Frequency**	**Cumulative Percent**
1.25G-1.25G	80	10.61	80	10.61
1.25G-PLACEBO	74	9.81	154	20.42
10G-10G	73	9.68	227	30.11
10G-PLACEBO	70	9.28	297	39.39
2.5G-2.5G	70	9.28	367	48.67
2.5G-PLACEBO	71	9.42	438	58.09
5G-5G	78	10.34	516	68.44
5G-PLACEBO	80	10.61	596	79.05
PLACEBO-1.25G	74	9.81	670	88.86
PLACEBO-2.5G	84	11.14	754	100.00

(Source: Reviewer based on randtrt data set)

The variation (minimum: 70, maximum: 84) between assignments to the different treatment sequences appears okay, given the large number of sites (each working with randomization assignments in blocks of ten). Note also, the randomization list is balanced between all ten possible treatment sequences.

Figure A3. ZS-004 Randomization (Maintenance Phase)

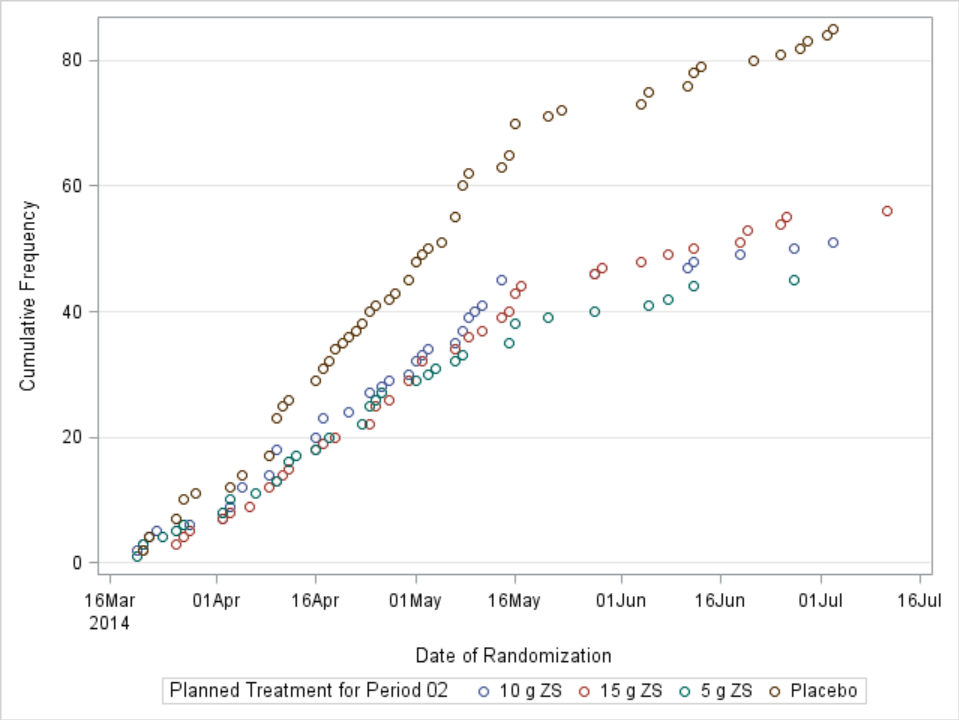


(Source: Reviewer)

Note the flattening out of the curves after May 16. The reason for this apparent slowing in the randomization is not clear.

Below is the same data displayed slightly differently (i.e., as a scatter plot). Note each circle represents a randomization date by treatment group (with one or more [max 6] subjects randomized at any specific date).

Figure A4. ZS-004 Randomization (Maintenance Phase)



(Source: Reviewer)

ZS-003 – More details regarding overall Type I error control for secondary endpoints?

SAP: "S-K at all time points" => interpreted in Study report as: "Mean change (absolute and percent) from baseline in S-K values". The sponsor picks first nominally stat significant time point compared to placebo (1 h for 10 g, 2 h for 5 g, 4 h for 2.5 g)

SAP:" Proportion of normokalemic subjects at 24 hours and 48 hours" => Study Report: uses all time points with measurements available

Order secondary endpoints were described in SAP does not match order results for those secondary endpoints are presented in Study Report => probably no fixed order of testing to start with (presentation of results below follows description in SAP)

Study report describes secondary endpoint results for 2.5 and 1.25 g doses including p-values, although both doses failed on primary endpoint (1.25 g in both acute and subacute phases, 2.5 g in subacute phase)

Table A2. ZS-003 Acute Phase: Secondary Endpoint

	ZS 10 g	**ZS 5 g**
S-K at all time points (Mean Change from BL)*	Nominally stat sign at <u>all</u> time points	Nominally stat sign at <u>some</u> time points
Time to normalization of S-K	Nominally stat sign	Not stat sign
Time to first decrease in S-K of 0.5 mmol/L	Nominally stat sign	Nominally stat sign
Proportion of normokalemic subjects at 24 hours and 48 hours	Nominally stat sign	Nominally stat sign

*No fixed testing procedure specified (assume testing in chronological order here)

Even when trying to give the sponsor the benefit of the doubt and "treating" the description in the SAP as pre-specified testing procedure, new issues arise as far as overall type I error control is concerned. For example conclusions regarding statistical significance will vary depending on whether one tests all endpoints for the 10 g dose first (could possibly claim four secondary endpoints for 10 g dose), and then moves on to the 5 g dose (and stops) or whether one tests the first secondary endpoint for 10 g dose and then for the 5 g dose (only win on first secondary endpoint for 10 g dose and stop).

It is not clear whether testing could proceed to the secondary endpoints in the subacute phase. The secondary endpoints mentioned in the SAP are included in the table below. The order of testing had not been specified in the SAP.

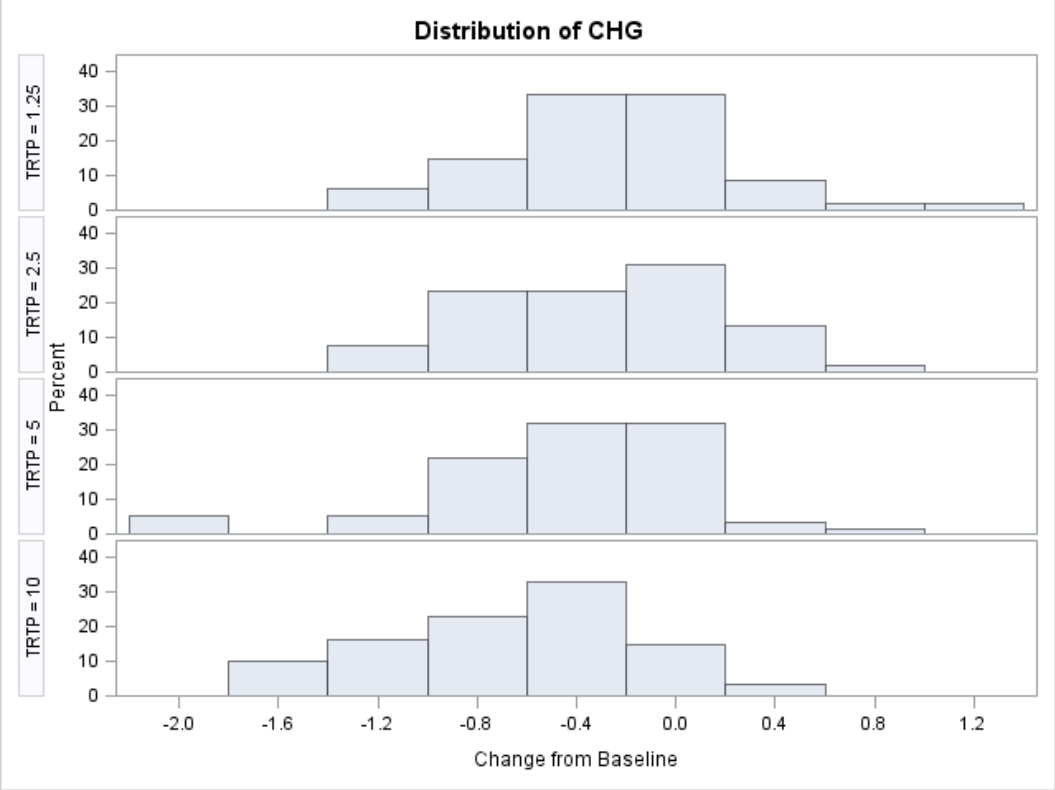
Table A3. ZS-003 Subacute Phase: Secondary Endpoints

	ZS 10 g	**ZS 5 g**
Maintaining normokalemic control (SK between 3.5 – 5.0)		
Total number of days maintaining normokalemic control	Nominally stat sign	Nominally stat sign
Proportion of patients remaining normokalemic at end of subacute phase	Nominally stat sign	Nominally stat sign
Time to a 0.5 mmol/L increase in S-K	Nominally stat sign	Not stat sign
Time to relapse (return to original S-K baseline)	Not stat sign	Nominally stat sign
S-K levels at other time points	Nominally stat sign at some time points	Not stat sign at any time points

Each test is versus placebo.

The layout of some possible hierarchical testing procedure above is all speculation – there is no pre-specified procedure to control the overall type I error rate for testing the secondary endpoints neither for the acute nor subacute phase in Study ZS-003. Testing of the secondary endpoints can only be considered exploratory.

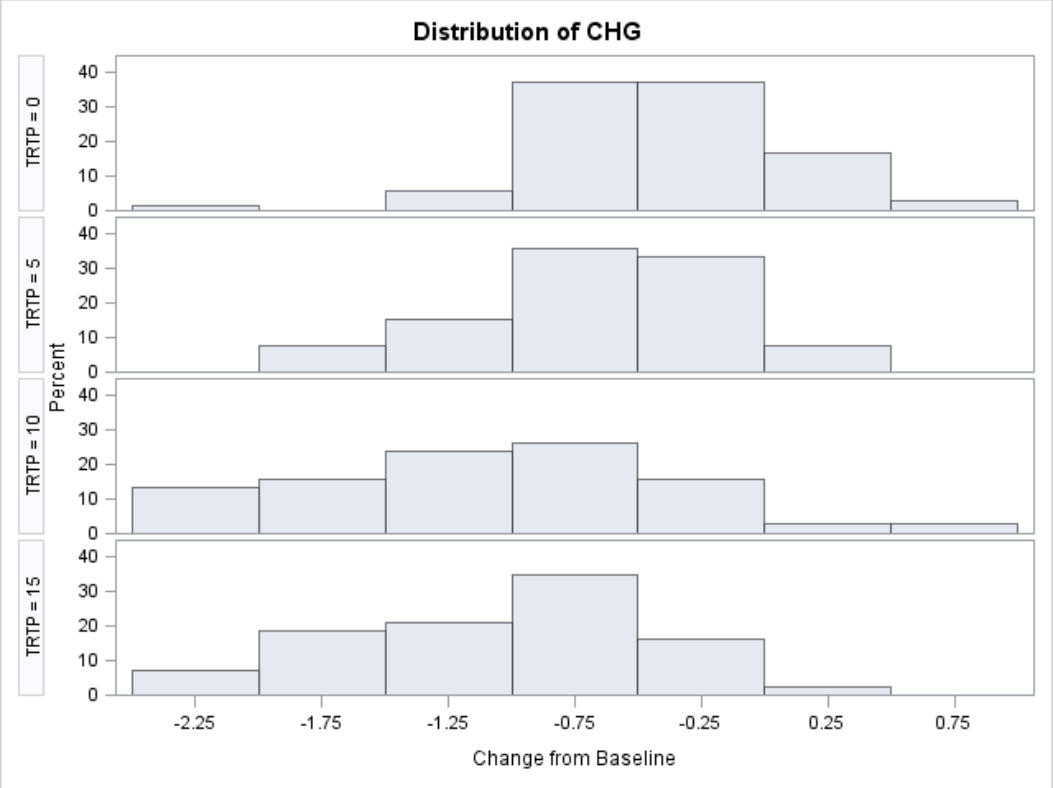
Figure A5. ZS-003 Potassium Change from Acute Phase Baseline (Day 0) to Day 15



[Source: Reviewer (SAS code: Potas_Histogram_Z003)]

Note: Each dose had its own placebo group in the subacute phase. The results for the placebo groups are not included in the histograms.

Figure A6. ZS-004 Potassium Change from Open Label Acute Phase Baseline (Day 0) to Day 29



[Source: Reviewer (SAS code: Potas_Histogram_Z004)]

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